EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	88	method adj4 agent adj consisting	US-PGPUB; USPAT; DERWENT	OR	OFF	2006/06/02 13:33
L2	43	method adj4 agent adj consisting	USPAT	OR	OFF	2006/06/02 14:14
L3	24	prevent adj cardiac adj arrhythmia	US-PGPUB; USPAT	OR	OFF	2006/06/02 14:16
L4	26	preventing adj cardiac adj arrhythmia	US-PGPUB; USPAT	OR	OFF	2006/06/02 14:40
L5	1	method adj2 treating adj cardiac adj toxicity	US-PGPUB; USPAT	OR	OFF	2006/06/02 14:47
L6	0	method adj2 treating adj cardiotoxicity	US-PGPUB; USPAT	OR	OFF	2006/06/02 14:47
L7	0	method adj2 treating adj2 cardiotoxicity	US-PGPUB; USPAT	OR	OFF	2006/06/02 14:47
L8	0	method adj2 treating adj3 cardiotoxicity	US-PGPUB; USPAT	OR	OFF	2006/06/02 14:47
L9	20	method adj4 cardiotoxicity	US-PGPUB; USPAT	OR	OFF	2006/06/02 14:50
L10	1009	cardiotoxicity	US-PGPUB; USPAT	OR	OFF	2006/06/02 14:50
L11	1324	cardiotoxicity or cardiotoxic	US-PGPUB; USPAT	OR	OFF	2006/06/02 14:50
L12	0	l11 and combrestatstatin	US-PGPUB; USPAT	OR	OFF	2006/06/02 14:50
L13	19	l11 and combretastatin	US-PGPUB; USPAT	OR	OFF	2006/06/02 14:52
L14	196	(chaplin or young) and combretastatin	US-PGPUB; USPAT	OR	OFF	2006/06/02 14:52
L15	40	l14 and propranolol	US-PGPUB; USPAT	OR	OFF	2006/06/02 14:53
L16	10	david adj chaplin	US-PGPUB; USPAT	OR	OFF	2006/06/02 14:55
L17	389	oxigene	US-PGPUB; USPAT	OR	OFF	2006/06/02 14:55
L18	113	l17 and combretastatin	US-PGPUB; USPAT	OR	OFF	2006/06/02 14:58
L19	73	l18 and (cardio or cardiotoxicity or cardiotoxic or arrhythmia or myocarditis or failure or cardiomyopathy or cardiac)	US-PGPUB; USPAT	OR	OFF	2006/06/02 14:56
L20	1	l18 and propranolol	US-PGPUB; USPAT	OR	OFF	2006/06/02 14:58

EAST Search History

L21	69	method adj2 preventing adj2 arrhythmia	US-PGPUB; USPAT	OR	OFF	2006/06/02 15:01

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     (FILE 'HOME' ENTERED AT 11:18:38 ON 02 JUN 2006)

     FILE 'REGISTRY' ENTERED AT 11:19:11 ON 02 JUN 2006
L1           35 S COMBRETASTATIN OR COMBRETASTATIN A 4 PHOSPHATE OR COMBRETASTA

     FILE 'CAPLUS, MEDLINE, BIOSIS, EMBASE' ENTERED AT 11:19:40 ON 02 JUN 2006
L2         1345 S L1
L3          101 S L2 AND (CARDIOTOXIC? OR CARDIO? OR HEART FAILURE OR MYOCARDIT
L4           88 DUP REM L3 (13 DUPLICATES REMOVED)
L5           88 FOCUS L4 1-
L6           22 S L2 AND (CARDIOTOXIC? OR CARDIOTOXICITY OR HEART FAILURE OR MY
L7           21 DUP REM L6 (1 DUPLICATE REMOVED)
L8           21 FOCUS L7 1-
L9          208 S L2 AND (ADVERSE EFFECT OR SIDE EFFECT OR TOXICITY OR UNDESIRE
L10          35 S L9 AND (CARDIO? OR CARDIOTOXICITY OR HEART FAILURE OR MYOPAT
L11          30 DUP REM L10 (5 DUPLICATES REMOVED)
L12          30 FOCUS L11 1-

     FILE 'USPATFULL, WPIX' ENTERED AT 11:31:51 ON 02 JUN 2006
L13         315 S L2
L14         149 S L13 AND L9
L15         146 DUP REM L14 (3 DUPLICATES REMOVED)
L16      278868 S CARDIOTOXICITY OR TOXICITY OR CARDIOTOXIC OR CARDIOMYOPATHY O
L17         128 S L15 AND L16
L18         128 FOCUS L17 1-
L19           8 S L18 AND (ANTIHYPERTENSIVE OR VASODILATOR OR BETA BLOCKER OR ?
L20        7642 S PROPRANOLOL
L21        1099 S L20 AND ((DRUG-INDUCED OR CHEMOTHERAPY) (L) (CARDIOTOXIC OR C
L22          73 S L21 AND CARDIOTOXICITY
L23          73 DUP REM L22 (0 DUPLICATES REMOVED)
L24          20 FOCUS L23 1-20

     FILE 'CAPLUS, MEDLINE, BIOSIS, EMBASE' ENTERED AT 11:47:40 ON 02 JUN 2006
L25          93 S L21
L26          16 S L25 AND CARDIOTOXICITY
L27          13 DUP REM L26 (3 DUPLICATES REMOVED)
L28          13 FOCUS L27 1-

=> d ibib abs hitstr l12 1-30

L12  ANSWER 1 OF 30  EMBASE  COPYRIGHT (c) 2006 Elsevier B.V. All rights
     reserved on STN
ACCESSION NUMBER:   2005231649  EMBASE
TITLE:              Vascular disrupting agents: A new class of drug in cancer
                    therapy.
AUTHOR:             Gaya A.M.; Rustin J.S.
CORPORATE SOURCE:   Dr. A.M. Gaya, The Clock Tower, Department of Medical
                    Oncology, Mount Vernon Cancer Centre, Rickmansworth Road,
                    Northwood, Middlesex HA6 1RU, United Kingdom.
                    andygaya@hotmail.com
SOURCE:             Clinical Oncology, (2005) Vol. 17, No. 4, pp. 277-290. .
                    Refs: 135
                    ISSN: 0936-6555  CODEN: CLIOEH
PUBLISHER IDENT.:   S 0936-6555(05)00015-4
COUNTRY:            United Kingdom
DOCUMENT TYPE:      Journal; General Review
FILE SEGMENT:       016     Cancer
                    030     Pharmacology
                    037     Drug Literature Index
                    038     Adverse Reactions Titles
LANGUAGE:           English
SUMMARY LANGUAGE:   English
ENTRY DATE:         Entered STN: 9 Jun 2005
                    Last Updated on STN: 9 Jun 2005
AB   Aims: To provide a comprehensive overview of the current state of
     development of a novel class of anti-cancer drugs, the vascular disrupting
     agents (VDAs), previously known as vascular targeting agents (VTAs).
     Materials and methods: A comprehensive review, analysis and com mentary of
     the published medical literature on VDAs was performed.  Results: Tumour
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vascular targeting therapy exploits known differences between normal and tumour blood vessels. VDAs target the pre-existing vessels of tumours (cf anti-angiogenics), and cause vascular shutdown leading to tumour cell death and rapid haemorrhagic necrosis within hours. It is becoming clear that VDAs have overlapping activity with anti-angiogenic drugs, which prevent the formation of new blood vessels. There are two types of VDA. First, biological or ligand-directed VDAs use antibodies, peptides or growth factors to target toxins or pro-coagulants to the tumour endothelium. In contrast, small molecule VDAs work either as tubulin-binding agents or through induction of local cytokine production. VDAs can kill tumour cells resistant to conventional chemotherapy and radiotherapy, and work best on cells in the poorly perfused hypoxic core of tumours, leaving a viable rim of well-perfused tumour tissue at the periphery, which rapidly regrows. Consequently, responses of tumours to VDAs given as single agents have been poor; however, combination therapy with cytotoxic chemotherapy, external-beam radiotherapy, and radioimmunotherapy, which target the peripheral tumour cells, has produced some excellent responses in animal tumours. VDAs are generally well tolerated with different **side-effect** profiles to current oncological therapies. Dynamic magnetic resonance imaging is most frequently used to obtain a pharmacodynamic end point to determine whether the VDA is acting on its intended target. Conclusions: VDAs are a promising new class of drug, which offer the attractive possibility of inducing responses in all tumour types with combination therapy.

L12 ANSWER 2 OF 30 EMBASE

ACCESSION NUMBER: 2004294920 EMBASE
TITLE: Vascular targeting agents.
AUTHOR: Pilat M.J.; McCormick J.; LoRusso P.M.
CORPORATE SOURCE: P.M. LoRusso, Karmanos Cancer Institute, 4100 John R, Detroit, MI 48201, United States. lorussop@karmanos.org
SOURCE: Current Oncology Reports, (2004) Vol. 6, No. 2, pp. 103-110. .
Refs: 56
ISSN: 1523-3790
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 29 Jul 2004
Last Updated on STN: 29 Jul 2004

AB The role of the vascular network of a tumor has been the focus of much recent research. Angiogenesis, or the growth of new tumor blood vessels, was initially the main target in the development of novel antitumor agents. More recently, new therapeutic strategies have been designed to destroy established tumor blood vessels. These vascular targeting agents (VTAs) exert their action by producing a rapid shutdown of tumor blood flow, resulting in ischemia and tumor cell necrosis. VTAs can be broadly divided into biologic agents and small molecules. In contrast to the biologic agents, drug-based vascular targeting molecules have developed much further, with many clinical trials ongoing. Evidence suggests that VTAs may be useful as single agents but can be more effective when used in combination with other therapeutic regimens.

L12 ANSWER 3 OF 30 EMBASE

ACCESSION NUMBER: 2004180571 EMBASE
TITLE: The Cancer Research UK experience of pre-clinical toxicology studies to support early clinical trials with novel cancer therapies.

AUTHOR: Newell D.R.; Silvester J.; McDowell C.; Burtles S.S.
CORPORATE SOURCE: J. Silvester, Drug Development Office, Cancer Research UK, PO Box 123, WC2A 3PX London, United Kingdom. julie.silvester@cancer.org.uk
SOURCE: European Journal of Cancer, (2004) Vol. 40, No. 6, pp. 899-906. .
Refs: 22
ISSN: 0959-8049 CODEN: EJCAEL
PUBLISHER IDENT.: S 0959-8049(04)00054-1
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
037 Drug Literature Index
038 Adverse Reactions Titles
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 6 May 2004
Last Updated on STN: 6 May 2004

AB Pre-clinical toxicology studies in rodents and Phase I clinical trial data are summarised for 14 novel anticancer therapies. With only one exception, an antifolate antimetabolite, rodent toxicology predicted a safe Phase I trial starting dose and the majority of the dose limiting **toxicities**, in particular haematological **toxicity**. For targeted agents with well-defined pharmacodynamic markers, illustrated in the current study by 3 anti-endocrine drugs and one resistance modifier, the definition of a maximum tolerated dose can be avoided. Together with earlier data, the current study confirms that pre-clinical toxicology studies in a non-rodent species are not routinely needed for the safe conduct of early clinical trials with new cancer chemotherapies.

L12 ANSWER 4 OF 30 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:49991 CAPLUS
DOCUMENT NUMBER: 141:167313
TITLE: **Cardiovascular** safety profile of combretastatin A4 phosphate in a single-dose phase I study in patients with advanced cancer
AUTHOR(S): Cooney, Matthew M.; Radivoyevitch, Tomas; Dowlati, Afshin; Overmoyer, Beth; Levitan, Nathan; Robertson, Kelly; Levine, Sandra L.; DeCaro, Kathleen; Buchter, Carol; Taylor, Anne; Stambler, Bruce S.; Remick, Scot C.
CORPORATE SOURCE: Department of Medicine, Division of Hematology/Oncology, Case Western Reserve University (CWRU), School of Medicine, Cleveland, OH, USA
SOURCE: Clinical Cancer Research (2004), 10(1, Pt. 1), 96-100
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The purpose of our study was to review and determine the **cardiovascular** safety profile of combretastatin A4 phosphate (CA4P) in a Phase I study in 25 patients with advanced solid tumors. CA4P was administered in a dose-escalating fashion starting at 18 mg/m2 i.v. every 21 days, and the maximal dosage was 90 mg/m2. Continuous evaluation included bedside blood pressure and pulse monitoring, 12-lead ECG at fixed time points for measured QT interval determination, determination of the corrected QT interval (QTc) using Bazett's formula QTc = QT/(R-R interval)1/2, and chart review. Pharmacodynamic correlations of CA4P dose, CA4P/CA4 area under the curve, and Cmax vs. heart rate (HR), blood pressure, QT, and QTc intervals, over the first 4 h postdosing were analyzed. After CA4P administration, there were significant increases in QTc interval at the 3-h and 4-h time points [27.2 ms ($P < 0.0001$) and 30.8 ms ($P < 0.0001$), resp.] and HR at the 3- and 4-h time points [13.2 beats per min (bpm; $P < 0.01$) and 15.1 bpm ($P < 0.001$), resp.]. Three of 25 patients had prolonged QTc intervals at baseline, whereas 15 (60%) of 25 and 18 (75%) of 24 patients had prolonged QTc intervals at 3 and 4 h. The slope of HR and QTc increasing as a function of time during the first 4 h was correlated to dose (in

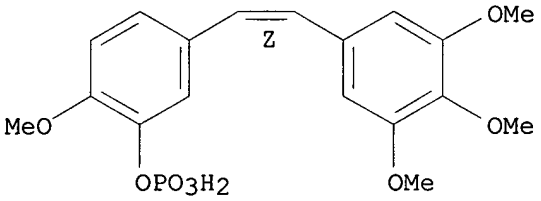
milligrams) of CA4P (P = 0.01 and r = 0.49 for HR, P = 0.005 and r = 0.55 for QTc) and to CA4 area under the curve (P = 0.04 and r = 0.41 for HR, P = 0.02 and r = 0.44 for QTc); blood pressure and uncorrected QTc interval dose-response correlations were not significant. Two patients had ECG changes consistent with an acute coronary syndrome within 24 h of CA4P infusion. CA4P prolongs the QTc interval. There was a temporal relation with the CA4P infusion and with ECG changes consistent with an acute coronary syndrome in two patients. It is advisable that future trials with CA4P have eligibility guidelines limiting patients with known coronary artery disease or those with multiple coronary artery disease risk factors until more experience is gained regarding potential **cardiovascular toxicity** with this agent.

IT **222030-63-9**, Combretastatin A4 phosphate
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tubulin inhibitor CA4 phosphate from Combretum caffrum increased action potential repolarization, QTc interval, HR and safe when administered alone without preexisting cardiac disease in phase I study of advanced solid tumor patient)

RN 222030-63-9 CAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, dihydrogen phosphate (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 5 OF 30 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2004133863 EMBASE
TITLE: [New pharmacological strategies for the treatment of cancer].
NOUVELLES APPROCHES PHARMACOLOGIQUES DE TRAITEMENT DES CANCERS.
AUTHOR: Buecher B.; Blottiere H.M.
CORPORATE SOURCE: B. Buecher, Serv. d'Hepato-Gastroenterologie, CHU de Nantes, Hotel-Dieu, place Alexis Ricordeau, 44093 Nantes Cedex 01, France. bruno.buecher@chu-nantes.fr
SOURCE: Gastroenterologie Clinique et Biologique, (2004) Vol. 28, No. 2, pp. 167-180. .
Refs: 119
ISSN: 0399-8320 CODEN: GCBIDC
COUNTRY: France
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
048 Gastroenterology
LANGUAGE: French
ENTRY DATE: Entered STN: 12 Apr 2004
Last Updated on STN: 12 Apr 2004
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L12 ANSWER 6 OF 30 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2004062718 EMBASE
TITLE: Vascular Targeting Agents As Cancer Therapeutics.
AUTHOR: Thorpe P.E.

CORPORATE SOURCE: P.E. Thorpe, Department of Pharmacology, Univ. Texas Southwestern Med. Ctr., H. C. Simmons Compreh. Cancer Ctr., 5323 Harry Hines Blvd., Dallas, TX 75390, United States. philip.thorpe@utsouthwestern.edu
SOURCE: Clinical Cancer Research, (15 Jan 2004) Vol. 10, No. 2, pp. 415-427. .
Refs: 142
ISSN: 1078-0432 CODEN: CCREF4
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 4 Mar 2004
Last Updated on STN: 4 Mar 2004

AB Vascular targeting agents (VTAs) for the treatment of cancer are designed to cause a rapid and selective shutdown of the blood vessels of tumors. Unlike antiangiogenic drugs that inhibit the formation of new vessels, VTAs occlude the pre-existing blood vessels of tumors to cause tumor cell death from ischemia and extensive hemorrhagic necrosis. Tumor selectivity is conferred by differences in the pathophysiology of tumor versus normal tissue vessels (e.g., increased proliferation and fragility, and up-regulated proteins). VTAs can kill indirectly the tumor cells that are resistant to conventional antiproliferative cancer therapies, i.e., cells in areas distant from blood vessels where drug penetration is poor, and hypoxia can lead to radiation and drug resistance. VTAs are expected to show the greatest therapeutic benefit as part of combined modality regimens. Preclinical studies have shown VTA-induced enhancement of the effects of conventional chemotherapeutic agents, radiation, hyperthermia, radioimmunotherapy, and antiangiogenic agents. There are broadly two types of VTAs, small molecules and ligand-based, which are grouped together, because they both cause acute vascular shutdown in tumors leading to massive necrosis. The small molecules include the microtubulin destabilizing drugs, combretastatin A-4 disodium phosphate, ZD6126, AVE8062, and Oxi 4503, and the flavonoid, DMXAA. Ligand-based VTAs use antibodies, peptides, or growth factors that bind selectively to tumor versus normal vessels to target tumors with agents that occlude blood vessels. The ligand-based VTAs include fusion proteins (e.g., vascular endothelial growth factor linked to the plant toxin gelonin), immunotoxins (e.g., monoclonal antibodies to endoglin conjugated to ricin A), antibodies linked to cytokines, liposomally encapsulated drugs, and gene therapy approaches. Combretastatin A-4 disodium phosphate, ZD6126, AVE8062, and DMXAA are undergoing clinical evaluation. Phase I monotherapy studies have shown that the agents are tolerated with some demonstration of single agent efficacy. Because efficacy is expected when the agents are used with conventional chemotherapeutic drugs or radiation, the results of Phase II combination studies are eagerly awaited.

L12 ANSWER 7 OF 30 EMBASE
ACCESSION NUMBER: 2004245743 EMBASE
TITLE: Anti-vascular tumor therapy: Recent advances, pitfalls and clinical perspectives.
AUTHOR: Eichhorn M.E.; Strieth S.; Dellian M.
CORPORATE SOURCE: M. Dellian, Institute for Surgical Research, Klinikum Grosshadern, University of Munich, Marchioninistrasse 15, D-81377 Munich, Germany. dellian@med.uni-muenchen.de
SOURCE: Drug Resistance Updates, (2004) Vol. 7, No. 2, pp. 125-138. .
Refs: 110
ISSN: 1368-7646 CODEN: DRUPFW
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index

038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 28 Jun 2004
Last Updated on STN: 28 Jun 2004

AB Anti-vascular tumor therapy represents a promising new strategy for cancer treatment. Anti-vascular treatment may be divided in anti-angiogenic and vascular targeting therapy. Whereas anti-angiogenic drugs aim on the inhibition of new vessel formation, vascular targeting compounds are designed to selectively destruct preexisting tumor blood vessels leading to secondary tumor cell death. Both anti-angiogenic drugs and vascular targeting agents have proven effective anti-tumoral activity in numerous preclinical studies over the last decade. In vivo, a combination with anti-vascular tumor therapy enhances the effects of other treatment modalities as chemo- and radiotherapy. Phase I clinical studies revealed a number of well-tolerated candidates. As monotherapy, however, anti-angiogenic treatment lacked efficacy in randomized clinical studies so far. In contrast, combination of anti-angiogenic therapy with chemotherapy was highly effective in an encouraging, large randomized phase III trial on metastatic colorectal cancer. This review will outline recent advances in the preclinical and clinical development of anti-vascular therapy with focus on vascular targeting. Conceptual differences between anti-angiogenic and vascular targeting therapies will be discussed with emphasis on specific problems and pitfalls in the conversion into the clinic. .COPYRGT. 2004 Elsevier Ltd. All rights reserved.

L12 ANSWER 8 OF 30 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2002217406 EMBASE
TITLE: A phase I pharmacokinetic and translational study of the novel vascular targeting agent combretastatin A-4 phosphate on a single-dose intravenous schedule in patients with advanced cancer.
AUTHOR: Dowlati A.; Robertson K.; Cooney M.; Petros W.P.; Stratford M.; Jesberger J.; Rafie N.; Overmoyer B.; Makkar V.; Stambler B.; Taylor A.; Waas J.; Lewin J.S.; McCrae K.R.; Remick S.C.
CORPORATE SOURCE: S.C. Remick, Univ. Hospitals of Cleveland, BHC-6, 11100 Euclid Avenue, Cleveland, OH 44106, United States
SOURCE: Cancer Research, (15 Jun 2002) Vol. 62, No. 12, pp. 3408-3416. .
Refs: 61
ISSN: 0008-5472 CODEN: CNREA8
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 8 Jul 2002
Last Updated on STN: 8 Jul 2002

AB Combretastatin A-4 phosphate (CA4P) is a novel antitumor vascular targeting agent, the first agent of this class of compounds to enter the clinic. We performed a Phase I trial to determine the maximum-tolerated dose, safety, and pharmacokinetic profile of CA4P on a single-dose i.v. schedule. We also obtained preliminary data on its effect on tumor blood flow using dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) techniques and cell adhesion molecules at the higher-dose levels. Twenty-five assessable patients with advanced cancer received a total of 107 cycles over the following dose escalation schema: 18, 36, 60, 90 mg/m(2) as a 10-min infusion and 60 mg/m(2) as a 60-min infusion at 3-week intervals. There was no significant myelotoxicity, stomatitis, or alopecia. Tumor pain was a unique **side effect**, which occurred in 10% of cycles, and there were four episodes of dose-limiting **toxicity** at dosages ≥60 mg/m(2), including two episodes of

acute coronary syndrome. Pharmacokinetics revealed rapid dephosphorylation of the parent compound (CA4P) to combretastatin A4 (CA4), with a short plasma half-life (30 min). A significant ($P < 0.03$) decline in gradient peak tumor blood flow by DCE-MRI in six of seven patients treated at 60 mg/m(2) was observed. A patient with anaplastic thyroid cancer had a complete response and is alive 30 months after treatment. The **toxicity** profile is consistent with a drug that is "vascularly active" and devoid of traditional "cytotoxic" **side effects**. Dosages ≤60 mg/m(2) as a 10-min infusion define the upper boundary of the maximum-tolerated dose.

L12 ANSWER 9 OF 30 EMBASE

ACCESSION NUMBER: 2004367274 EMBASE
TITLE: Multiple endocrine neoplasia type 2.
AUTHOR: Gertner M.E.; Kebebew E.
CORPORATE SOURCE: Dr. E. Kebebew, Department of Surgery, Univ. of California San Francisco, 1600 Divisadero Street, San Francisco, CA 94115, United States. kebebewe@surgery.ucsf.edu
SOURCE: Current Treatment Options in Oncology, (2004) Vol. 5, No. 4, pp. 315-325. .
Refs: 43
ISSN: 1527-2729 CODEN: CTOOBW
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
016 Cancer
022 Human Genetics
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 16 Sep 2004
Last Updated on STN: 16 Sep 2004

AB Multiple endocrine neoplasia type 2 (MEN-2) is a hereditary syndrome that is transmitted in an autosomal dominant pattern. MEN-2A, MEN-2B, and familial medullary thyroid cancer (MTC) comprise the MEN-2 syndrome. A germline mutation in the RET proto-oncogene is responsible for the MEN-2 syndrome. Recent data indicate that in 99% of MEN-2 cases, a germline RET mutation can be identified by genetic testing. The phenotypic variation of MEN-2 is diverse and partly related to the codon and specific point mutation in the RET proto-oncogene. There are increasing data on the genotype-phenotype correlations in patients with MEN-2 and this information should be used for screening at-risk patients and treatment of RET mutation carriers. All patients (especially if young) with MTC or bilateral pheochromocytoma should have a careful family history taken and genetic screening for RET germline mutations. Patients who are RET germline mutation carriers but without clinical or biochemical evidence of MTC should have a prophylactic total thyroidectomy. The optimal age of thyroidectomy should be based on the RET genotype (eg, high-risk mutations [codons 634, 883, 918, and 922] within the first year of life, intermediate-risk mutations [codons 611, 618, and 620] by 5 years of age, and low-risk mutations [codons 609, 630, 768, 790, 791, 804, and 891] by 10 years of age). Patients who are diagnosed with clinical or biochemical evidence of MTC should have a total or a near total thyroidectomy and at least a central neck lymph node dissection. Patients who have pheochromocytoma and a unilateral adrenal tumor on a localizing study should have a unilateral laparoscopic adrenalectomy after preoperative α-blockade. However, patients with bilateral adrenal tumors on localizing studies should have bilateral laparoscopic adrenalectomy. A cortical-sparing (subtotal) adrenalectomy may be considered, if technically feasible, to avoid long-term steroid dependence and to reduce the risk of Addisonian crisis. Patients with biochemical evidence of primary hyperparathyroidism should have a bilateral neck exploration and total parathyroidectomy and autotransplantation (30-60 mg of the most normal parathyroid tissue) to the nondominant forearm if asymmetric parathyroid hyperplasia is present. Rarely, patients may have only single-gland disease and excision may be performed if the other

parathyroid glands are not found with biopsy to be hyperplastic. All unresected parathyroid glands should be marked with a clip because patients with MEN-2A have a high risk of persistent and recurrent primary hyperparathyroidism. Patients with familial MTC may have not manifested the other features of MEN-2A, thus these patients should have continued follow-up for pheochromocytoma and primary hyperparathyroidism. Copyright .COPYRGT. 2004 by Current Science Inc.

L12 ANSWER 10 OF 30 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2004149963 EMBASE
TITLE: Combretastatin A4 phosphate.
AUTHOR: West C.M.L.; Price P.
CORPORATE SOURCE: P. Price, Acad. Dept. of Radiation Oncology, Christie NHS Trust Hospital, Wilmslow Road, Manchester M20 4BX, United Kingdom. pat.price@man.ac.uk
SOURCE: Anti-Cancer Drugs, (2004) Vol. 15, No. 3, pp. 179-187. .
Refs: 83
ISSN: 0959-4973 CODEN: ANTDEV
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 014 Radiology
016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 6 May 2004
Last Updated on STN: 6 May 2004

AB Combretastatin A4 phosphate (CA4P) is a water-soluble prodrug of combretastatin A4 (CA4). The vascular targeting agent CA4 is a microtubule depolymerizing agent. The mechanism of action of the drug is thought to involve the binding of CA4 to tubulin leading to cytoskeletal and then morphological changes in endothellal cells. These changes increase vascular permeability and disrupt tumor blood flow. In experimental tumors, anti-vascular effects are seen within minutes of drug administration and rapidly lead to extensive ischemic necrosis in areas that are often resistant to conventional anti-cancer treatments. Following single-dose administration a viable tumor rim typically remains from which tumor regrowth occurs. When given in combination with therapies targeted at the proliferating viable rim, enhanced tumor responses are seen and in some cases cures. Results from the first clinical trials have shown that CA4P monotherapy is safe and reduces tumor blood flow. There has been some promising demonstration of efficacy. CA4P in combination with cisplatin is also safe. Functional imaging studies have been used to aid the selection of doses for phase II trials. Both dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and positron emission tomography can measure the anti-vascular effects of CA4P in humans. This review describes the background to the development of CA4P, its proposed mechanism of action, the results from the first clinical trials with CA4P and the role of imaging techniques in its clinical development. .COPYRGT. 2004 Lippincott Williams & Wilkins.

L12 ANSWER 11 OF 30 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2006:40252 CAPLUS
DOCUMENT NUMBER: 144:444736
TITLE: Novel vascular targeting/disrupting agents: combretastatin A4 phosphate and related compounds
AUTHOR(S): Cooney, Matthew M.; Ortiz, Jose; Bukowski, Ronald M.; Remick, Scot C.
CORPORATE SOURCE: Developmental Therapeutics Program, Case Comprehensive Cancer Center, University Hospitals of Cleveland and Cleveland Clinic, Cleveland, OH, 44106, USA
SOURCE: Current Oncology Reports (2005), 7(2), 90-95
CODEN: CORUAT; ISSN: 1523-3790
PUBLISHER: Current Science Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

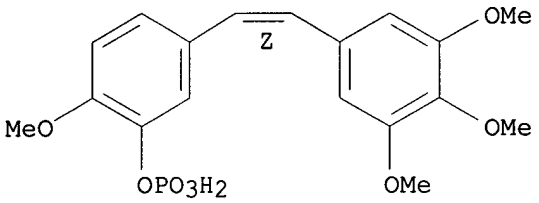
AB A review. Novel anticancer compds. are being developed that attempt to exploit the unique properties of the vascular endothelium, which supplies rapidly dividing neoplasms. The goal of these vascular targeting agents (VTAs) or endothelial disrupting agents is to cause rapid shutdown of tumor blood supply with subsequent tumor death from hypoxia and nutrient deprivation. VTAs are classified into two broad categories: biol. therapies or small mol. compds. A variety of VTAs are in early clin. development. These agents have demonstrated clin. activity in phase I trials and are being evaluated with cytotoxic chemotherapy and radiotherapy.

IT **222030-63-9**, Combretastatin A4 phosphate
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(vascular targeting agents like combretastatin A4 phosphate is to cause rapid shutdown of tumor blood supply with subsequent tumor death from hypoxia and nutrient deprivation but demonstrated potential **cardiovascular toxicity** in human)

RN 222030-63-9 CAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, dihydrogen phosphate (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 12 OF 30 EMBASE

ACCESSION NUMBER: 2005235690 EMBASE
TITLE: Use of angiogenesis inhibitors in tumour treatment.
AUTHOR: Fayette J.; Soria J.-C.; Armand J.-P.
CORPORATE SOURCE: J.-P. Armand, Institut Gustave Roussy, Departement de Medecine, 39 Rue Camille Desmoulins, 94805 Villejuif, France. armand@igr.fr
SOURCE: European Journal of Cancer, (2005) Vol. 41, No. 8, pp. 1109-1116. .
Refs: 53
ISSN: 0959-8049 CODEN: EJCAEL
PUBLISHER IDENT.: S 0959-8049(05)00185-1
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 30 Jun 2005
Last Updated on STN: 30 Jun 2005

AB Advances in molecular biology have permitted the characterisation of mechanisms underlying angiogenesis. Angiogenesis is a crucial process in tumour pathogenesis as it sustains malignant cells with nutrients and oxygen. It is well known that tumour cells secrete various growth factors including VEGF, which triggers endothelial cells to form new capillaries. Preventing the expansion of new blood vessel networks results in reduced tumour size and metastases. Not surprisingly, numerous drugs that are currently under clinical development interfere with growth factor-derived angiogenic signals. This review aims to describe angiogenesis inhibitors and surveys their different modes of action.

L12 ANSWER 13 OF 30 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2003410858 EMBASE
TITLE: Microtubules, microtubule-interfering agents and apoptosis.
AUTHOR: Mollinedo F.; Gajate C.
CORPORATE SOURCE: F. Mollinedo, Centro de Investigacion del Cancer, Inst. Biol. Molec./Cel. del Cancer, CSIC-Universidad de Salamanca, E-37007 Salamanca, Spain. fmollin@usal.es
SOURCE: Apoptosis, (2003) Vol. 8, No. 5, pp. 413-450. .
Refs: 463
ISSN: 1360-8185 CODEN: APOPFN
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 30 Oct 2003
Last Updated on STN: 30 Oct 2003

AB Microtubules are dynamic polymers that play crucial roles in a large number of cellular functions. Their pivotal role in mitosis makes them a target for the development of anticancer drugs. Microtubule-damaging agents suppress microtubule dynamics, leading to disruption of the mitotic spindle in dividing cells, cell cycle arrest at M phase, and late apoptosis. A better understanding of the processes coupling microtubule damage to the onset of apoptosis will reveal sites of potential intervention in cancer chemotherapy. Inhibition of microtubule dynamics induces persistent modification of biological processes (M arrest) and signaling pathways (mitotic spindle assembly checkpoint activation, Bcl-2 phosphorylation, c-Jun NH(2)-terminal kinase activation), which ultimately lead to apoptosis through the accumulation of signals that finally reach the threshold for the onset of apoptosis or through diminishing the threshold for engagement of cell death. Microtubules serve also as scaffolds for signaling molecules that regulate apoptosis, such as Bim and survivin, and their release from microtubules affect the activities of these apoptosis regulators. Thus, sustained modification of signaling routes and changes in the scaffolding properties of microtubules seem to constitute two major processes in the apoptotic response induced by microtubule-interfering agents.

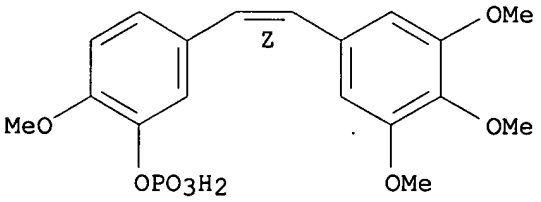
L12 ANSWER 14 OF 30 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2004517874 EMBASE
TITLE: Molecular targeting: Targeting angiogenesis in solid tumors.
AUTHOR: Soria J.-C.; Fayette J.; Armand J.-P.
CORPORATE SOURCE: J.-C. Soria, Institut Gustave Roussy, Departement de Medecine, Villejuif, France
SOURCE: Annals of Oncology, (2004) Vol. 15, No. SUPPL. 4, pp. iv223-iv227. .
Refs: 38
ISSN: 0923-7534 CODEN: ANONE2
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
026 Immunology, Serology and Transplantation
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
ENTRY DATE: Entered STN: 28 Dec 2004
Last Updated on STN: 28 Dec 2004
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L12 ANSWER 15 OF 30 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:942007 CAPLUS

DOCUMENT NUMBER: 142:253877
TITLE: Phase I trial of the antivascular agent combretastatin A4 phosphate on a 5-day schedule to patients with cancer: magnetic resonance imaging evidence for altered tumor blood flow
AUTHOR(S): Stevenson, James P.; Rosen, Mark; Sun, Weijing; Gallagher, Maryann; Haller, Daniel G.; Vaughn, David; Giantonio, Bruce; Zimmer, Ross; Petros, William P.; Stratford, Michael; Chaplin, David; Young, Scott L.; Schnall, Mitchell; O'Dwyer, Peter J.
CORPORATE SOURCE: University of Pennsylvania Cancer Center, Philadelphia, PA, USA
SOURCE: Journal of Clinical Oncology (2003), 21(23), 4428-4438
CODEN: JCONDN; ISSN: 0732-183X
PUBLISHER: American Society of Clinical Oncology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Purpose: Combretastatin A4 (CA4) phosphate (CA4P) inhibits microtubule polymerization and is toxic to proliferating endothelial cells in vitro. It causes reversible vascular shutdown in established tumors in vivo, consistent with an antivascular mechanism of action. The present study investigated escalating doses of CA4P administered i.v. to patients with advanced cancer. Patients and Methods: Patients with solid malignancies and good performance status received CA4P as a 10-min infusion daily for 5 days repeated every 3 wk. Pharmacokinetic sampling was performed during cycle 1. Patients receiving ≥ 52 mg/m2/d had serial dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) studies to measure changes in tumor perfusion with CA4P treatment. Results: Thirty-seven patients received 133 treatment cycles. CA4P dose levels ranged from 6 mg/m2 to 75 mg/m2 daily. Severe pain at sites of known tumor was dose limiting at 75 mg/m2. Dose-limiting **cardiopulmonary toxicity** (syncope and dyspnea or hypoxia) was noted as well in two patients treated at 75 mg/m2. Other **toxicities** included hypotension, ataxia, dyspnea, nausea or vomiting, headache, and transient sensory neuropathy. Plasma CA4P and CA4 area under the concentration-time curve and maximal concentration values increased linearly with dose. Tumor perfusion, as measured by the first-order rate constant of gadolinium plasma to tissue transfer during DCE-MRI studies, was found to decrease in eight of 10 patients. Relationships were also demonstrated between perfusion changes and pharmacokinetic indexes. A partial response was observed in a patient with metastatic soft tissue sarcoma, and 14 patients exhibited disease stability for a min. of two cycles. Conclusion: Doses of CA4P on a daily times five schedule of 52 to 65 mg/m2 were reasonably well-tolerated. The 52 mg/m2 dose is recommended for further study based on cumulative phase 1 experience with CA4P. Antitumor efficacy was observed, and the use of DCE-MRI provided a valuable noninvasive measure of the vascular effects of CA4P treatment.
IT **222030-63-9**, Combretastatin A4 phosphate
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(altered tumor blood flow induced by antivascular agent combretastatin A4 phosphate on a 5-day schedule to patients with cancer)
RN 222030-63-9 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, dihydrogen phosphate (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS

L12 ANSWER 16 OF 30 EMBASE

ACCESSION NUMBER: 2006092825 EMBASE
TITLE: Vascular-targeting agents and radiation therapy in lung cancer: Where do we stand in 2005?.
AUTHOR: Raben D.; Ryan A.
CORPORATE SOURCE: Dr. D. Raben, Tobacco-Related Malignancy Program, Department of Radiation Oncology, University of Colorado Health Sciences Center, Box 6510, Aurora, CO 80010-0510, United States. david.raben@uchsc.edu
SOURCE: Clinical Lung Cancer, (2005) Vol. 7, No. 3, pp. 175-179. .
Refs: 49
ISSN: 1525-7304 CODEN: CLCLCA
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 014 Radiology
015 Chest Diseases, Thoracic Surgery and Tuberculosis
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 10 Mar 2006
Last Updated on STN: 10 Mar 2006

AB With recent Food and Drug Administration approval of the anti-vascular endothelial growth factor (VEGF) antibody for the treatment of colon cancer, it may be possible to achieve similar progress in the treatment of locally advanced lung cancer. Antiangiogenic therapies in the clinic are a reality, and it is important to demonstrate that they can be used safely with conventional modalities, including radiation therapy (RT). Strategies under scrutiny in preclinical and clinical studies include the use of endogenous inhibitors of angiogenesis, use of agents that target VEGF and VEGF receptor signaling, targeting endothelial-related integrins during angiogenesis, and targeting the preexisting immature vessels growing within tumors (ie, vascular targeting). Regardless of the approach, it is necessary to address whether angiogenesis is a consistent phenomenon within the lung parenchyma around a cancer and a relevant target and whether inhibiting angiogenesis will improve current lung cancer therapies without increasing **toxicity**. Vascular-targeting agents (VTAs) are an interesting class of agents that have the potential to enhance RT, but their clinical promise has yet to be realized. In preclinical models, these agents selectively destroy the tumor vasculature, initiating a rapid centralized necrosis within established tumors. Characteristically, after treatment with VTAs, a rim of viable tumor cells remains at the periphery of the tumor, which remains well perfused and should therefore be relatively sensitive to radiation-induced cytotoxicity. This review will focus on VTAs in the treatment of lung cancer and includes a discussion of combination studies with RT in the laboratory and some of the hurdles in the clinical application of these agents.

L12 ANSWER 17 OF 30 EMBASE

ACCESSION NUMBER: 2004220040 EMBASE
TITLE: [Medical treatment of haemangiomas].
TRATAMIENTO MEDICO DE LOS HEMANGIOMAS.
AUTHOR: Lloret P.
CORPORATE SOURCE: P. Lloret, Departamento de Dermatologia, Clinica Universitaria, Apdo. 4209, 31080 Pamplona, Spain. plloret@unav.es
SOURCE: Anales del Sistema Sanitario de Navarra, (2004) Vol. 27, No. SUPPL. 1, pp. 81-92. .
Refs: 77
ISSN: 1137-6627 CODEN: ASSNFO
COUNTRY: Spain
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer

018 Cardiovascular Diseases and Cardiovascular Surgery
027 Biophysics, Bioengineering and Medical Instrumentation
037 Drug Literature Index
038 Adverse Reactions Titles

LANGUAGE: Spanish
SUMMARY LANGUAGE: English; Spanish
ENTRY DATE: Entered STN: 10 Jun 2004
Last Updated on STN: 10 Jun 2004

AB There are two clearly differentiated attitudes in the treatment of haemangiomas: the expectant attitude and the therapeutic, medical or surgical attitude. The expectant attitude can be appropriate in cases of small haemangiomas, far from areas of possible functional damage, and with a slow rate of growth; however, it must be remembered that after reaching their maximum involution, about 25% of haemangiomas show a significant deformity. Treatment should be applied to those haemangiomas that obstruct the visual axis, the airway, the auditory channel, (with alteration of functions such as vision, breathing, swallowing and urinary or intestinal functions); to those of rapid growth that produce or might produce tissue destruction or significant disfiguration, ulcerated lesions, and lesions with a great cutaneous extension or visceral affection, which can lead to congestive cardiac insufficiency, or haematological alterations. The recommended treatment is systemic corticosteroids, with an initial dose of 2 to 3 mg/kg/day of prednisone or prednisolone, administered once a day in the morning. The most frequent result is that growth is arrested, while a reduction in size is observed in less than half the cases. Intralesional administration of corticosteroids at intervals of between 4 and 8 weeks is an effective treatment that manages to avoid the **adverse effects** of systemic corticosteroids. Because of its adverse neurological effects, interferon is only recommended for lesions with a vital or severe functional risk that do not respond to corticosteroids. Cytotoxic drugs are another treatment group: intralesional bleomycin, vincristine, cyclophosphamide and pingiangmycin. Finally, other forms midway between medical and surgical treatment, such as intermittent compression, radiotherapy, cryotherapy, sclerotherapy, or the implantation of intralesional metals, might have a role to play in some specific haemangiomas.

L12 ANSWER 18 OF 30 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2003:153852 BIOSIS
DOCUMENT NUMBER: PREV200300153852
TITLE: The First International Conference on Vascular Targeting: Meeting overview.
AUTHOR(S): Thorpe, Philip E. [Reprint Author]; Chaplin, David J.; Blakey, David C.
CORPORATE SOURCE: Department of Pharmacology, University of Texas Southwestern Medical Center, Dallas, TX, 75390, USA philip.thorpe@utsouthwestern.edu
SOURCE: Cancer Research, (March 1 2003) Vol. 63, No. 5, pp. 1144-1147. print.
ISSN: 0008-5472 (ISSN print).
DOCUMENT TYPE: Article
Conference; Report; (Meeting Report)
LANGUAGE: English
ENTRY DATE: Entered STN: 26 Mar 2003
Last Updated on STN: 26 Mar 2003

AB The First International Conference on Vascular Targeting focused on vascular targeting agents (VTAs) that occlude or destroy the pre-existing blood vessels of solid tumors. The VTAs cause a rapid shutdown in the blood supply to the tumor that kills tumor cells by depriving them of oxygen and nutrients. The VTAs are distinct from antiangiogenic agents, which prevent new blood vessel formation. Two major types of VTAs are being developed for cancer: the ligand-directed VTAs that use antibodies, peptides, and growth factors to deliver toxins, procoagulants, and proapoptotic effectors to tumor endothelium, and the small molecule VTAs that do not specifically localize to tumor endothelium but exploit pathophysiological differences between tumor and normal tissue endothelia

to induce acute vascular shutdown in tumors. Both approaches were described at the meeting and highlighted the variety of VTAs in preclinical development, their selectivity for tumor endothelium, their rapid antitumor effects, and the improved activity seen when combined with other anticancer approaches (antiproliferative chemotherapeutic drugs, radiation, radiolabeled antibodies, nitric oxide synthetase inhibitors, and anti-angiogenic agents). Early clinical studies were summarized for the small molecule VTAs: the antitubulin drugs, combretastatin A4 phosphate (CA4P) and ZD6126, and the flavonoid, 5,6-dimethylxanthenone-4-acetic acid (DMXAA). The agents lacked the bone marrow and gastrointestinal **toxicities** associated with antiproliferative chemotherapy. As a marker of biological effect, blood flow reductions in tumors were measured using magnetic resonance imaging or positron emission tomography for all of the agents tested, and single-agent clinical activity was seen. These agents are now being evaluated in combined modality studies to see whether the impressive results obtained in experimental models can be translated into humans.

L12 ANSWER 19 OF 30 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2000:162241 BIOSIS
DOCUMENT NUMBER: PREV200000162241
TITLE: The new tubulin-inhibitor combretastatin A-4 enhances thermal damage in the BT4An rat glioma.
AUTHOR(S): Eikesdal, Hans Petter [Reprint author]; Schem, Baard-Christian; Mella, Olav; Dahl, Olav
CORPORATE SOURCE: Department of Oncology, Haukeland Hospital, University of Bergen, 5021, Bergen, Norway
SOURCE: International Journal of Radiation Oncology Biology Physics, (Feb. 1, 2000) Vol. 46, No. 3, pp. 645-652. print.
CODEN: IOBPD3. ISSN: 0360-3016.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 26 Apr 2000
Last Updated on STN: 4 Jan 2002

AB Purpose: To investigate the **toxicity** of combretastatin A-4 disodium phosphate (CA-4) and its vascular effects in the subcutaneous (s.c.) BT4An rat glioma, and additionally, to determine the tumor response of CA-4 combined with hyperthermia. Methods and Materials: For assessment of drug **toxicity**, rats were given 50, 75, or 100 mg/kg CA-4 and followed by daily registration of weight and **side effects**. Interstitial tumor blood flow was determined by laser Doppler flowmetry in rats injected with 50 mg/kg CA-4. In the tumor response study we administered CA-4 50 mg/kg alone or combined with hyperthermia (waterbath 44degreeC for 60 min) 0 or 3 h later. Results: We found that CA-4, at a well-tolerated dose of 50 mg/kg, induced a considerable time-dependent decrease in the tumor blood flow. Tumor blood flow was reduced by 47-55% during the first 110 min after injecting CA-4, and thereafter remained decreased until the measurements were terminated. Administering CA-4 3 h before hyperthermia yielded the best tumor response and increased tumor growth time significantly compared with simultaneous administration of CA-4 and hyperthermia ($p = 0.03$). Interestingly, CA-4 alone did not influence tumor growth. Conclusion: CA-4 induces a gradual reduction in tumor blood flow which can be exploited to sensitize the BT4An tumor for hyperthermia.

L12 ANSWER 20 OF 30 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2006216764 EMBASE
TITLE: Tumor vasculature: The Achilles' heel of cancer?.
AUTHOR: Mocellin S.
CORPORATE SOURCE: S. Mocellin, Department of Oncological and Surgical Sciences, School of Medicine, University of Padova, via Giustiniani 2, 35128 Padova, Italy
SOURCE: International Journal of Cancer Research, (2006) Vol. 2, No. 2, pp. 176-187. .
Refs: 33
ISSN: 1811-9727 E-ISSN: 1811-9735
COUNTRY: Pakistan

DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 29 May 2006
Last Updated on STN: 29 May 2006

AB Given its pivotal role in growth and survival, the tumor vasculature represents an attractive target for anticancer therapy. Over the last few decades, rapid progress has been achieved in the understanding of tumor angiogenesis including signaling pathways and their regulation. This has enabled the development of numerous potentially effective vasculature-targeted anticancer drugs (VTAD), which are being tested in the clinical setting. In this review I will focus on the most promising and advanced drugs targeting the tumor vasculature, briefly summarizing their mechanism of action and the clinical results so far obtained.

L12 ANSWER 21 OF 30 EMBASE
ACCESSION NUMBER: 2004048447 EMBASE
TITLE: Angiogenesis and Anti-angiogenesis therapeutics: 20-21 February 2002, London, UK.
AUTHOR: Mazucco R.A.
CORPORATE SOURCE: R.A. Mazucco, Current Drugs Ltd., Middlesex House, 34-42 Cleveland Street, London W1 4LB, United Kingdom. roy.mazucco@current-drugs.com
SOURCE: IDrugs, (2002) Vol. 5, No. 4, pp. 320-322. .
ISSN: 1369-7056 CODEN: IDRUFN
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 12 Feb 2004
Last Updated on STN: 12 Feb 2004

AB The potential for pro- and anti-angiogenic drugs is great. The market for a number of indications that these drugs promise relief for is large and in some cases unmet. It remains as no great surprise that a number of companies are investing great amounts of money in trying to tap into the potential gains. Despite the innovation of the drugs being developed, it is almost certain that in order for them to achieve the efficacy required to treat today's diseases, they will need to be used in combination with other therapies, and studies indicate that some anti-angiogenic drugs are less efficacious when used as a monotherapy. Overall, this was a fulfilling meeting that yet only scratched the surface of an exciting new therapeutic area with great future potential.

L12 ANSWER 22 OF 30 CAPLUS
ACCESSION NUMBER: 2004:690510 CAPLUS
DOCUMENT NUMBER: 141:235461
TITLE: Combretastatin A4 phosphate: background and current clinical status
AUTHOR(S): Young, Scott L.; Chaplin, David J.
CORPORATE SOURCE: OXiGENE, Inc., Waltham, MA, 02451, USA
SOURCE: Expert Opinion on Investigational Drugs (2004), 13(9), 1171-1182
CODEN: EOIDER; ISSN: 1354-3784
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Combretastatin A4 phosphate (CA4P) represents the lead compound

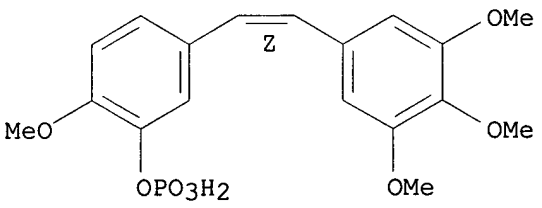
in a group of novel tubulin depolymg. agents being developed as vascular targeting agents (VTAs). VTAs are drugs that induce rapid and selective vascular dysfunction in tumors. CA4P is a water-soluble prodrug of the cis-stilbene CA4 originally isolated from the tree Combretum caffrum. Preclin. studies have shown that CA4P induces blood flow redns. and subsequent tumor cell death in a variety of preclin. models. Moreover, this activity has been linked to its ability to rapidly alter the morphol. of immature endothelial cells by disrupting their tubulin cytoskeleton. Phase I clin. trials have established a maximum tolerated dose in the range 60-68 mg/m2 and in addition have established that significant changes to tumor perfusion can be achieved across a wide range of doses. The dose-limiting **toxicities** include tumor pain, ataxia and **cardiovascular** changes. The maximum tolerated dose was independent of schedule, indicating the absence of cumulative **toxicity**. Although unexpected from preclin. studies, some evidence of clin. response was seen using CA4P as a single modality. Based on the Phase I data, combination studies of CA4P with established therapies are in progress and should determine whether the exciting preclin. data obtained when VTAs are used in combination with cytotoxic chemotherapy, radiation, radioimmunotherapy and even antiangiogenic agents, can be translated into man.

IT **222030-63-9**, Combretastatin A4 phosphate
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor combretastatin A4 phosphate)

RN 222030-63-9 CAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, dihydrogen phosphate (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 23 OF 30 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2002:220869 BIOSIS
DOCUMENT NUMBER: PREV200200220869
TITLE: Inhibition of proliferative retinopathy by the anti-vascular agent combretastatin-A4.
AUTHOR(S): Griggs, Jeremy; Skepper, Jeremy N.; Smith, Gerry A.; Brindle, Kevin M.; Metcalfe, James C.; Hesketh, Robin [Reprint author]
CORPORATE SOURCE: Department of Biochemistry, University of Cambridge, Tennis Court Rd., Cambridge, CB2 1QW, UK
t.r.hesketh@bioc.cam.ac.uk
SOURCE: American Journal of Pathology, (March, 2002) Vol. 160, No. 3, pp. 1097-1103. print.
CODEN: AJPAA4. ISSN: 0002-9440.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Apr 2002
Last Updated on STN: 3 Apr 2002

AB Retinal neovascularization occurs in a variety of diseases including diabetic retinopathy, the most common cause of blindness in the developed world. There is accordingly considerable incentive to develop drugs that target the aberrant angiogenesis associated with these conditions. Previous studies have shown that a number of anti-angiogenic agents can inhibit retinal neovascularization in a well-characterized murine model of ischemia-induced proliferative retinopathy. Combretastatin-A4 (CA-4) is an anti-vascular tubulin-binding agent currently undergoing clinical

evaluation for the treatment of solid tumors. We have recently shown that CA-4 is not tumor-specific but elicits anti-vascular effects in nonneoplastic angiogenic vessels. In this study we have examined the capacity of CA-4 to inhibit retinal neovascularization in vivo. CA-4 caused a dose-dependent inhibition of neovascularization with no apparent **side effects**. The absence of vascular abnormalities or remnants of disrupted neovessels in retinas of CA-4-treated mice suggests an anti-angiogenic mechanism in this model, in contrast to the anti-vascular effects observed against established tumor vessels. Importantly, histological and immunohistochemical analyses indicated that CA-4 permitted the development of normal retinal vasculature while inhibiting aberrant neovascularization. These data are consistent with CA-4 eliciting tissue-dependent anti-angiogenic effects and suggest that CA-4 has potential in the treatment of nonneoplastic diseases with an angiogenic component.

L12 ANSWER 24 OF 30 EMBASE

ACCESSION NUMBER: 2005064723 EMBASE
TITLE: Gateways to clinical trials: December 2004.
AUTHOR: Bayes M.; Rabasseda X.; Prous J.R.
CORPORATE SOURCE: M. Bayes, Prous Science, P.O. Box 540, 08080 Barcelona, Spain. mbayes@prous.com
SOURCE: Methods and Findings in Experimental and Clinical Pharmacology, (2004) Vol. 26, No. 10, pp. 801-827. .
Refs: 163
ISSN: 0379-0355 CODEN: MFEPDX
COUNTRY: Spain
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 006 Internal Medicine
017 Public Health, Social Medicine and Epidemiology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 24 Feb 2005
Last Updated on STN: 24 Feb 2005

AB Gateways to Clinical Trials is a guide to the most recent clinical trials in current literature and congresses. The data in the following tables has been retrieved from the Clinical Studies Knowledge Area of Prous Science Integrity®, the drug discovery and development portal, http://integrity. prous.com. This issue focuses on the following selection of drugs: Abetimus sodium, ademetionine, agalsidase alfa, agalsidase beta, alemtuzumab, alfimeprase, AMG-162, androgel, anidulafungin, antigastrin therapeutic vaccine, aripiprazole, atomoxetine hydrochloride; Bazedoxifene acetate, bevacizumab, bosentan; Caldaret hydrate, canfosfamide hydrochloride, choriogonadotropin alfa, ciclesonide, combretastatin A-4 phosphate, CY-2301; Darbepoetin alfa, darifenacin hydrobromide, decitabine, degarelix acetate, duloxetine hydrochloride; ED-71, enclomiphene citrate, eplerenone, epratuzumab, escitalopram oxalate, eszopiclone, ezetimibe; Fingolimod hydrochloride, FP-1096; HMR-3339A, HSV-TK/GCV gene therapy, human insulin, HuOKT3gamma1(Ala234-Ala235); Idursulfase, imatinib mesylate, indiplon, InnoVax C insulin glargine, insulin glulisine, irofulven; Labetuzumab, lacosamide, lanthanum carbonate, LyphoDerm, Lyprinol; Magnesium sulfate, metelimumab, methylphenidate hydrochloride; Natalizumab, NO-aspirin; OROS(R); PC-515, pegaptanib sodium, peginterferon alfa-2a, peginterferon alfa-2b, peginterferon alfa-2b/ribavirin, pemetrexed disodium, peptide YY3-36, posaconazole, pregabalin, PT-141, pyridoxamine; R-744, ramelteon, ranelic acid distrontium salt, rebimastat, repinotan hydrochloride, rhC1, rhGAD65, rosiglitazone maleate/metformin hydrochloride; Sardomozide, solifenacin succinate; Tadalafil, taxus, telavancin, telithromycin, tenofovir disoproxilfumarate, teriparatide, testosterone transdermal patch, tetomilast, tirapazamine, torcetrapib; Valspodar, vardenafil hydrochloride hydrate, vildagliptin; Yttrium Y90 epratuzumab; Ziprasidone hydrochloride. .COPYRGT. 2004 Prous Science. All rights reserved.

L12 ANSWER 25 OF 30 BIOSIS

STN
ACCESSION NUMBER: 1997:168391 BIOSIS
DOCUMENT NUMBER: PREV199799474994
TITLE: Effects of novel and conventional anti-cancer agents on human endothelial permeability: Influence of tumour secreted factors.
AUTHOR(S): Watts, Margaret E. [Reprint author]; Woodcock, Michael; Arnold, Stephanie; Chaplin, David J.
CORPORATE SOURCE: Tumour Microcirculation Group, Gray Lab. Cancer Res. Trust, P.O. Box 100, Mount Vernon Hosp., Northwood HA6 2JR, Middlesex, UK
SOURCE: Anticancer Research, (1997) Vol. 17, No. 1A, pp. 71-75. CODEN: ANTRD4. ISSN: 0250-7005.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Apr 1997
Last Updated on STN: 24 Apr 1997

AB A number of anti-cancer agents have been implicated in vascular **toxicity**. The effects have been attributed to direct drug **toxicity** towards endothelium. Little attention has been focussed on the ineraction between anticancer drugs, endothelial cells and tumour secreted factors. It is well known that tumours can secrete factors such as vascular permeability factor which do affect endothelial cells and could alter their response to the vascular effects of anticancer drugs. In the present study, we have examined, in vitro, the direct effects of vinblastine (VBL), 5-fluorouracil (5-FU), melphalan (L-PAM) and the novel tubulin inhibitor combretastatin A-1 (CBS) on endothelial permeability under normal and tumour simulated conditions. Monolayers of human umbilical vein endothelial cells (HUVEC) grown on membrane filters were incubated in drug in normal growth medium or medium conditioned by the human melanoma cell line, RPMI-7951 (TCM). VBL caused a rapid increase in permeability during the first 20 minutes, which was maintained for the duration of the experiment (120 minutes). The effect was not altered by TCM or restored to control levels when VBL was replaced by drug-free medium. Similarly, CBS caused a rapid increase in permeability; however, in contrast to VBL, this increase was enhanced by TCM. The changes induced by VBL and CBS were accompanied by contraction of the endothelial F-actin cytoskeleton. Neither L-PAM nor 5-FU altered the permeability of HUVEC monolayers. This study demonstrates that certain anti-cancer agents have a direct effect on endothelial cells, leading to an increase in the permeability of endothelial monolayers. Both VBL and CBS have vascular components in their mode of action which may lead to vascular collapse and tumour necrosis.

L12 ANSWER 26 OF 30 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1997:261915 BIOSIS
DOCUMENT NUMBER: PREV199799568518
TITLE: Combretastatin A-4, an agent that displays potent and selective **toxicity** toward tumor vasculature.
AUTHOR(S): Dark, Graham G. [Reprint author]; Hill, Sally A.; Prise, Vivien E.; Tozer, Gillian M.; Pettit, George R.; Chaplin, Dai J.
CORPORATE SOURCE: Tumour Microcirculation Group, Gray Lab. Cancer Res. Trust, Mount Vernon Hosp., Northwood, Middlesex HA6 2JR, UK
SOURCE: Cancer Research, (1997) Vol. 57, No. 10, pp. 1829-1834. CODEN: CNREA8. ISSN: 0008-5472.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Jun 1997
Last Updated on STN: 24 Jun 1997

AB Selective induction of vascular damage within tumors represents an emerging approach to cancer treatment. Histological studies have shown that several tubulin-binding agents can induce vascular damage within tumors but only at doses approximating the maximum tolerated dose, which has limited their clinical applicability. In this study, we show that the combretastatin A-4 prodrug induces vascular shutdown within tumors at doses less than one-tenth of the maximum tolerated dose. In vitro studies indicate that a short drug exposure results in profound long-term

antiproliferative/cytotoxic effects against proliferating endothelial cells but not cells that are quiescent prior to and during drug exposure. Vascular shutdown, within experimental and human breast cancer models in vivo following systemic drug administration, was demonstrated with a reduction in functional vascular volume of 93% at 6 h following drug administration and persisted over the next 12 h, with corresponding histology consistent with hemorrhagic necrosis resulting from vascular damage. These actions against tumor vasculature and the broad therapeutic window demonstrate the clinical potential of these drugs and warrant further study to elucidate the mechanisms responsible for the antivascular effects of combretastatin A-4.

L12 ANSWER 27 OF 30 EMBASE

ACCESSION NUMBER: 2006052660 EMBASE
TITLE: Potential of PET in oncology and radiotherapy.
AUTHOR: Saleem A.
CORPORATE SOURCE: Dr. A. Saleem, Clatterbridge Centre for Oncology, Wirral, United Kingdom
SOURCE: British Journal of Radiology, (2005) Vol. 78, No. SUPPL. 28, pp. 6-16. .
Refs: 52
ISSN: 0007-1285 CODEN: BJRAAP
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
023 Nuclear Medicine
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 3 Mar 2006
Last Updated on STN: 3 Mar 2006

AB In summary, in addition to its use and value in RTP and research, functional imaging with PET can be utilised in a variety of applications for the research and therapy of cancer. Its value in the elucidation of pathophysiological processes, development of anticancer drugs and as a response and prognostic indicator is likely to increase by the day. PET imaging and data interpretation is truly multidisciplinary, requiring co-operation between animal biologists, pharmacologists, physicists, PET technicians, data modellers, radiochemists and clinicians. Finally, the importance of development and validation of methodology and the need for carefully planned studies prior to the universal adoption of novel radioligands, methodology and machines cannot be over emphasised. Functional PET imaging has tremendous potential and we need to harness it in order to use it successfully. .COPYRGT. 2005 The British Institute of Radiology.

L12 ANSWER 28 OF 30 EMBASE

ACCESSION NUMBER: 2003407674 EMBASE
TITLE: Endothelial cells as therapeutic targets in cancer: New biology and novel delivery systems.
AUTHOR: Murray J.C.; Moghimi S.M.
CORPORATE SOURCE: Dr. J.C. Murray, CRUK Tumour Cytokine Biology Group, Wolfson Digestive Diseases Centre, University Hospital, Nottingham NG7 24H, United Kingdom. cliff.murray@nott.ac.uk
SOURCE: Critical Reviews in Therapeutic Drug Carrier Systems, (2003) Vol. 20, No. 2-3, pp. 139-152. .
Refs: 68
ISSN: 0743-4863 CODEN: CRTSEO
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
039 Pharmacy
LANGUAGE: English

SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 30 Oct 2003
Last Updated on STN: 30 Oct 2003

AB The significance of the endothelial cell as a target for antitumor therapy has been recognized for some time, but so far the results of clinical trials exploiting this approach have not been encouraging. The subject is likely to gain new momentum, however, following a number of important recent findings that shed new light on the origins and nature of tumor vasculature. Coupled with rapid developments in the use of phage-displayed peptide libraries to characterize the human vascular map, as well as highly selective delivery systems, this new understanding of tumor vascular biology should provide many fresh and exciting avenues to explore.

L12 ANSWER 29 OF 30 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2005378699 EMBASE
TITLE: Lignans and neolignans as lead compounds.
AUTHOR: Apers S.; Vlietinck A.; Pieters L.
CORPORATE SOURCE: L. Pieters, Department of Pharmaceutical Sciences, University of Antwerp, Universiteitsplein 1, B-2610 Antwerp, Belgium. luc.pieters@ua.ac.be
SOURCE: Phytochemistry Reviews, (2003) Vol. 2, No. 3, pp. 201-217. .
Refs: 56
ISSN: 1568-7767 CODEN: PRHEBS
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 004 Microbiology
016 Cancer
030 Pharmacology
037 Drug Literature Index
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 22 Sep 2005
Last Updated on STN: 22 Sep 2005

AB Many lignans and neolignans have served as lead compounds for the development of new drugs. Perhaps the best known example is podophyllotoxin, an antimitotic compound that binds to tubulin. Etoposide and teniposide are derived from podophyllotoxin, but their antitumoural activity is due to inhibition of topoisomerase II. Combination of both pharmacophores has led to compounds with a dual mechanism of action, such as azatoxin. Dihydrobenzofuran neolignans, based on the natural lead 3',4-di-O-methylcedrusin, have also been investigated as potential antitumoural agents; the dimerisation product of caffeic acid methyl ester was the most active compound. Here too, he cytotoxic activity was due to inhibition of tubulin polymerisation. In addition, the same compounds showed antiangiogenic activity. Podophyllotoxin, as well as other types of lignans, such as dibenzylbutyrolactones related to arctigenin, dibenzocyclooctadiene-type lignans, and dibenzylbutanes, have been explored as leads for antiviral agents (also including HIV). Synthetic 8.O.4'- neolignans have been evaluated for their antileishmanial and antifungal properties. Detailed study of the antifungal properties of the phenylpropanoid moieties has resulted in the design of highly active arylpropanoid derivatives. Other examples where lignans have been used as lead compounds include enzyme inhibitors of phosphodiesterase IV and V, and 5-lipoxygenase, and for the development of hypolipidemic and antirheumatic agents. .COPYRGT. 2004 Kluwer Academic Publishers.

L12 ANSWER 30 OF 30 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2003277454 EMBASE
TITLE: New approaches to cancer therapy.
AUTHOR: Garattini S.
CORPORATE SOURCE: S. Garattini, Istituto Ricerche Farmacol. M. Negri, Milano, Italy. mapelli@marionegri.it
SOURCE: Annals of Oncology, (1 Jun 2003) Vol. 14, No. 6, pp. 813-816. .

Refs: 56
ISSN: 0923-7534 CODEN: ANONE2
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Editorial
FILE SEGMENT: 016 Cancer
030 Pharmacology
036 Health Policy, Economics and Management
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
ENTRY DATE: Entered STN: 31 Jul 2003
Last Updated on STN: 31 Jul 2003
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

Combretastatin Update 1: in Ohio Phase I Trial, Some Tumors Respond, Patients Experience Vascular Stress

November 8, 1999 /PSA Rising/ Early results from a Phase I clinical trial of **combretastatin** A4 (CA4P) show that the drug can starve tumors of their blood supply and does shrink some solid tumors. One patient so far who took the drug for about six months obtained a complete remission.

Combretastatin does not, apparently, cause two of the commoner side-effects of chemo -- low blood counts and hair loss. But even at the lowest doses given in this Ohio trial, **Combretastatin** has caused tumor pain. At higher doses in some patients it caused lung and heart stress.

Combretastatin may prove more effective then some standard chemotherapy drugs and in some respects easier to tolerate. But as one of the first anti-vascular cancer drugs to be tested on humans, it has been hyped. The idea of shrinking tumors by attacking their life support system has been championed by Judah Folkman, a physician and cancer researcher at Children's Hospital in Boston who has received worldwide attention for his work. Like endostatin and angiostatin, Dr. Folkman's discoveries, **Combretastatin** apparently causes no distress at all in mice.

On the basis of this Ohio Phase I trial -- designed to test mainly for **toxicity** but watching, obviously, for efficacy -- **combretastatin** begins to look more ordinary.

Combretastin comes from a substance found in the bark of an African willow. It is the first novel antitumor vascular-targeting agent to enter clinical testing. In preclinical, laboratory studies in animals, University of Florida researchers reported last November, it boosted the tumor-cell killing power of radiation therapy as much as 500 times. It was found to be synergistic also with Taxol.

Phase I clinical trials of **combretastatin** alone, in what at the time were called "small doses," began last November at the Ireland Cancer Center at University Hospitals of Cleveland, Ohio. Other arms of the trial began at Pennsylvania Cancer Center and at Mount Vernon Hospital in Hammersmith, London, UK. The London trial still plans to try to escalate to twice the dose found to be tolerable for humans in Ohio.

Tumor Pain and Cardiac Symptoms

One of the patients in the Ohio trial was featured this fall in a US News & World Report article about the promise of innovative cancer therapies. Scott C. Remick. M.D. at Ireland Cancer Center is in charge of the Ohio trial. Last week Dr. Remick reported preliminary results at the XVII annual Chemotherapy Foundation Symposium in New York. I asked him more about this patient. Dr. Remick said the patient completed 10 3-week cycles and withdrew from the trial with a "complete response."

As an anti-angiogenic agent, **combretastatin** has a major impact on tumor blood vessels. As well as messing up microtubule assembly (like taxol and other drugs) it also "attacks proliferating endothelial cells," Dr. Remick said. Animal studies showed "immediate shutdown" of blood vessels supplying the tumor but no apparent effect on other blood vessels. The drug acts quickly, peaking at 6 hours with effects sustained for 24 hours.

Combretastatin sets off a process of apoptosis (death of damaged cells) in the tumor blood vessels, Dr. Remick said last week. And as it cuts off the tumor's blood supply, **combretastatin** also kills cancer cells (induces tumor necrosis) starting in the core of the tumor and radiating out.

In Ohio, 19 men and woman have been treated so far. The patients took **combretastatin** intravenously once every 3 weeks (in Pennsylvania the dosing is once a day for 5 days on 3 week cycles). Most of them had had prior chemotherapy. They took thsi drug as a 10 minute IV infusion "in a light-protected environment." Doses ran from 18 mg/m2 to 90 mg/m2. Dr. Remick found **combretastatin** to be effective at 60 mg/m2 and toxic at 90/mg/ml2.

Results look fairly promising except for side-effects. Out of the 19 patients, one patient with osteosarcoma and another with non-small cell lung cancer got 12-week partial responses. The osteosarcoma patient showed blood flow changes in tumor in bone in the hip area. A patient with renal cell cancer got 24 weeks of stable disease. A 55 year-old man with anaplastic thyroid cancer got the best result. He was able to take 10 cycles, over a period of about thirty weeks, and achieved a "complete" remission visible on scans.

Humans Respond Differently Than Mice

What are the side effects of the attack on tumor blood vessels? For several hours following infusion, across all dose levels, Dr. Remick reported last week, his patients experienced a "variable symptom complex." Faint flush, abdominal pain and other pain at the sites of known tumor occurred at all dose levels during the infusion. Nausea and vomiting occurred at higher doses and also fever, flush, lightheadedness, headache, diarrhea, bradycardia (slowed heart beat), tachychardia (rapid heart beat) transient blood pressure changes and "non-specific ST-T wave changes on electrocardiogram, which peak between 3 and 5 hours post-infusion."

Although none of these side-effects were considered to be dose-limiting, tumor pain was "significant," Dr. Remick said. even more of a damper on some of the euphoric publicity surrounding blood-vessel targeting cancer therapies. **Toxicity** occurred at dose level 4 (90 mg/m2). One patient had an episode of "grade 3 pulmonary **toxicity** (shortness of breath)." Another, after only two doses, experienced a "reversible episode" of "acute coronary ischemia" thought to be secondary to "coronary vasospasm."

Toxicities of this order are not unusual for potent chemotherapies -- although more typical of allergic reactions. But **combretastatin** was promoted so enthusiastically before the trial, these results look rather disappointing.

Dietmar Siemann, a professor of radiation oncology in UF's College of Medicine, said last year, before the trial began, that results from combining **combretastatin**

with radiation "are very encouraging." (see our story Nov 1998)."We're able to achieve these effects by giving relatively low doses that produce no side effects in mice." he said. A lot depends, though, on what mice feel. Mice are mot, initially at least, apprehensive about taking a drug for cancer that may bring on sensations of heart attack.

"The **combretastatin** approach is a little different from what Dr. Folkman has been doing," Siemann said last November. "The majority of research has focused on preventing the growth of new tumor blood vessels, the anti-angiogenesis strategy. What we are doing is attacking existing and newly formed tumor blood vessels directly by exploring a key difference between these vessels and those found in normal tissues." "We and others have shown." Siemman said, "that these dividing cells can be selectively damaged by **combretastatin**. This approach leads to rapid and catastrophic shutdown in the vessels that serve the tumor, resulting in extensive tumor cell death."

The theory was, this type of therapy would be both more effective and tolerable for human cancer patients than ordinary chemo. The Ohio investigators plan to try giving **combretastatin** as a one hour infusion instead of ten minutes (less of a shock to the body). They will continue to investigate the cardiac effects.

See earlier article, **Combretastatin, from African Bush Willow, in Early Trials** *November 23, '98.*

*The Ohio Phase I trial of **combretastatin** is supported by a clinical research grant from **OXiGENE,** Inc., Boston, MA. Results were reported November 5, 1999 at Chemotherapy Foundation Symposium XVII "Innovative Cancer Therapy for Tomorrow" in New York.*

Dr. Scot C. Remick, M.D. is program leader for developmental therapeutics at the Ireland Cancer Center, Cleveland and associate professor of medicine at Case Western Reserve University School of Medicine.

*Dietmar Siemann, of the Moffitt Cancer Center in Tampa, published a paper on their work on **Combretastatin** in the November 1998 issue of the* **International Journal of Radiation Oncology, Biology, Physics.**

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November 8, 1999; page last modified June 20, 2001

PSA Rising

prostate cancer survivor news

institutCurie
Together, let's beat cancer.

Conception, synthesis and targeting of biomolecules - UMR 176 CNRS/Institut Curie

Bioorganic chemistry, drug targeting

Group leader : Jean-Claude Florent

The research efforts of our group have been primarily focused toward the conception and synthesis of antitumor agents, and also toward the improvement of the bioavailability and the targeting of anticancer drugs by several approaches (ADEPT, PMT, immuno-conjugates). Emphasis has also been placed on the targeting of topoisomerases I and II inhibitors to the genes implicated in cell growth, or to anti-apoptosis genes through triple-helix formation. The programme concerning the development of angiogenesis inhibitors and the targeting of these agents to tumor vasculature is being pursued.
The elaboration of small molecules which block protein-protein interactions implicated in cancer is a a new common theme in our department. Finally, we have initiated a study on the intracellular transport of the sub-unit B of SHIGA toxin and its application to intracellular targeting within the framework of a program at the chemistry-biology interface.

I. Molecules acting on angiogenesis

This project is part of a Curie Research Programme (PIC).

1 Antivascular compounds and targeting (R. Pontikis, C. Monneret). Participants : J. Guillaumel, J. Kaffy. (*Collaboration : A. Commerçon, P. Maillet, Aventis*).

Angiogenesis (i.e.: formation of new blood vessels from those pre-existing) is a fundamental process in tumor development. For this reason, it constitutes a novel strategy in anticancer chemotherapy. Two parallel strategies have been developed: one based on the inhibition of newly-formed vessels (anti-angiogenesis); the other, more recent, on the development of therapies specifically aimed at the destruction of the tumor vasculature.
As blood vessels in tumors have different phenotypes from that of normal tissues (proliferation rate, modified tubulin, interactions between cytoskeletons of tubuline and actin, and micro-environmental factors...) they are selectively recognized by certain inhibitors of tubulin polymerization. They have thus the property (at doses less that the maximum doses which can be administered) to induce destruction of these vessels with necrosis of endothelial cells and induction of severe hypoxia.

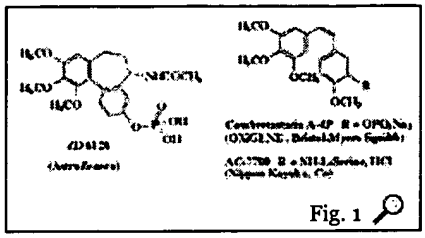

Fig. 1

Preclinical data for **combretastatin** A4-phosphate shows that it exerts a limited action when used alone, but its activity is enhanced by combined administration with radiotherapy or classical chemotherapy. Other limiting factors are: (1) the relative instability of the molecule, and (2) its recognized **cardiotoxicity**. Thus, our goal was to find novel inhibitors of tubulin polymerization which would be more efficient, more stable, and less toxic, and to try to better understand their mechanism of action. In this context, we have synthesized a series of conformationally rigid **combretastatin** analogues wherein the central double bond was replaced by a different heterocycles. A hybrid combretastatine-thalidomide analogue was also synthesized.

2. Analogues of flavon-8-acetic acid (D. Dauzonne). Participant : J.-B. Bongui. *(Collaboration : B. Bauvois U 365 INSERM).*

Flavone-8- acetic acid (FAA), inhibits endothelial cell proliferation *in vitro* and selectively destroys tumor vasculature, leading to tumor cell death by ischemia. It has also been established, in mice, that immune system cells participate in tumor necrosis induced by this compound.
Over the past three years, several pertinent findings in the field of angiogenesis have led to a renewal of interest in flavones: certain flavonoids are able to regulate MMP-9 (Matrix Metalloproteinase-9) and VEGF (Vascular Endothelium Growth Factor) expression.

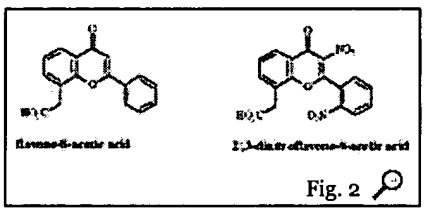

Fig. 2

Using the original route developed by our group to obtain flavones, we have prepared various novel 3-nitro and 3-amino FAA derivatives. It was found that most of these flavones are not cytotoxic, and that 2',3'-dinotroflavone-8-acetic acid is a specific, reversible and competitive inhibitor of ectoprotease APN/CD13. Further experiments showed that this derivative can inhibit APN/CD13 activity in monocytes U937, as well as in myeloid cell lines (THP-1, HL-60 and MonoMac6), T (Jurkat) and B (Ramos, Eskol, RPMI8266) lymphoids, and monocytes and lymphocytes isolated from circulating blood. The inhibitory effect of this compound was also seen on solid tumor cells (Ewing sarcoma, melanoma).
In a collaboration with Dr J. Soria (PH AP, Hôtel-Dieu, Paris) *in vitro* angiogenesis assays will be used to measure the ability of our compounds to block the formation of capillary tubes in HUVEC cells cultivated on matrigel and fibrin. For the *in vivo* tests, we shall use the "CAM assay" which measures the formation of capillary tubes in the chorio-allantoic membrane of embryos. If these tests are positive, further cancer tests using nude mice will be planed.
Further, several flavone samples were supplied to Prof. J. Langner (Martin-Luther University Halle-Wittenberg Institute of Medical Immunology, Halle, Germany) who requested them with the intention of co-crystallizing them with APN/CD13.

II Targeting of anticancer agents (F. Schmidt, J.-C. Florent, C. Monneret, M. Azoulay)

1. Prodrug Mono Therapy (PMT) :

***a) Taxol, Taxotere, Campthothecin and Etoposide* (F. Schmidt, C. Monneret)**
Participants : E. Bouvier, S. Angenault. *(Collaboration : P. Renard, ADIR)*

***b) Epothilone* (F. Schmidt, C. Monneret, J-C Florent).**
Participants : A. El Alaoui. N. Saha. *(Collaboration : K. Bosslet (Schering)).*

Improvement of the selectivity of anticancer agents toward cancer cells remains a major challenge in anticancer chemotherapy. Our laboratory has invested heavily in the development of the two-step ADEPT (Antibody Directed Enzyme Prodrug Therapy) strategy for drug targeting. In this technique the distribution of a cytotoxic agent is modified by generating it selectively in the tumor: first targeting an enzyme at the tumor cell surface in the form of a fusion protein (Mab humanized anti-CEA for the targeting, and human-β-glucuronidase for the catalytic enzyme reaction), then injecting a non-toxic prodrug hydrolysed by this enzyme, thus enabling the release of the anticancer agent.

From the work realized in collaboration with the Behring Institute at Marburg (Germany), it rapidly appeared that the HMR 1826 prodrug synthesized at Curie could spontaneously liberate doxorubicin from necrotic tumors. This fact led us to propose a new strategy called PMT (Prodrug Mono Therapy). Besides this, histological studies demonstrated a very high level of β-glucuronidase activity in the necrotic areas. In continuation of this program, we synthesized a prodrug of etoposide (or Vepeside®). The biological results concerning its solubility (more hydrophilic than Etopophos®), its serum stability and its enzymatic hydrolysis parameters were sufficiently encouraging to lead us to deposit an European Patent (Institut Curie). This approach has been extended to other microtubule-stabilizing agents (Taxol®, Taxotere®, Epothilone), and to compounds stabilizing the ternary complex topoisomerase I-campthothecin-DNA.

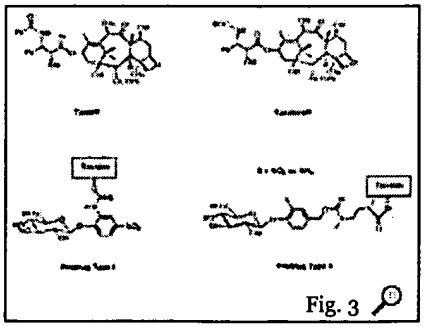
Fig. 3

The Taxol case appeared more complex. Due to its fragility and bulk, we were led to imagine a new self-immolative spacer. These studies allowed us to publish the two first prodrugs of Taxotere® able to be enzymatically activated. The preliminary biological experiments demonstrated good kinetics for the release of Taxotere. Concerning Campthothecin, two major problems have been encountered in clinic: its poor solubility and its high toxicity. This led to the development of the more soluble drug Irinotecan,® or CPT 11, prodrug which, in human, is converted into SN38, the active metabolite, under the action of liver esterases. However, esterase hydrolysis was not site-specific. These reasons prompted us to synthesize, in collaboration with the Servier Institute, four new SN38 glucuronylated prodrugs which are currently under investigation. Our acquired knowledge in this field led us to collaborate with Schering to extend the approach to a very cytotoxic drug, Epothilone. For this compound we elaborated several glucuronide phenyl-glycoside or glucuronyl carbamate spacers. These spacers, which can be cleaved by β-glucuronidase will be coupled to epothilone. The main difficulties encountered in this field was associated with final deprotection which had to be done in conditions compatible with the stability of the molecule. This work is in continuation.

2. Vectorisation of epothilones by formation of immuno-conjugates (J.-C. Florent, C. Monneret). Participant : E. Meneses

Epothilones A and B, like Taxol® and Taxotere®, induce microtubule assembly and stabilization, even in cell lines resistant to taxanes. However, they present the advantage of being more soluble. Due to the very pronounced cytotoxicity of these natural products (and synthetic analogues) they are excellent models for immuno-targeting. The recent approval by the FDA (USA) of an immunoconjugate associating the antibody Anti-CD33 and calicheamicin (an enediyne antibiotics producing DNA double-strand breaks at picomolar concentrations) for the treatment of acute myeloid leukemia serves to demonstrate the importance of this approach.
In collaboration with Schering AG (Berlin), we initiated a project to synthesize immuno-conjugates of new epothilone derivatives with monoclonal antibodies for targeting the neo-angiogenesis of tumors (Tumor Endothelium-Activated-Prodrug Therapy). It is anticipated that this approach will offer several advantages since endothelial cells are easily accessible, and the destruction of one vessel will result in the destruction of thousands of tumor cells. It is therefore unnecessary to destroy each endothelial cell around the tumor (association with other cytotoxic agents). Moreover, endothelial cells are genetically stable, thus less susceptible of developing resistance. Anti-vascular therapy can be used on diverse solid tumors using highly overexpressed endothelial markers. Several spacers which bind to a monoclonal, VEGF anti-receptor antibody, have been prepared in our group and are currently under study at Schering.

3. Targeting and activation of antitumor compounds with the B-subunit of Shiga toxin (J.-C. Florent, F. Schmidt). (Participants : A. El Alaoui.) *(Collaboration : L. Johannes (UMR 144 Curie)* within a Curie "PIC" Research Programme*).*

In continuation of our effort on drug targeting (ADEPT, PMT, Immuno-conjugate) we have recently established a collaboration with L. Johannes (UMR 144, Curie Institute) to use a modified form of Shiga toxin B-subunit STxB-Z(n)-Cys as a tool for vectorisation. The modified B-subunit possesses an added cystein residue at the C-terminal that can be used as a "cargo" to selectively release cyctotoxic drugs at glycosphingolipid Gb3-presenting cells. This glycosphingolipid is a tumor antigen present in intestinal and colorectal tumors ($CACO_2$ tumor cell line). We wish to take advantage of two unique features of this toxin: (1) the selective recognition of Gb3, which is overexpressed on the cell surface, 2) the selective intracellular targeting of the Golgi apparatus (retrograde pathway) which, in principle, may permit selective activation of a prodrug by resident enzymes in this cell compartment. Considering that the group of D. Louvard and S. Robine (UMR 144) possesses an excellent murin model for the study of the development of colon cancer which overexpresses Gb3, it will be possible to rapidly evaluate the therapeutic potential of this strategy to target anticancer agents like Campthothecin, Taxol, Taxotere that are used in clinic. The synthesis of a non-toxic 4-compartment prodrug system and its ligation with the B-Shiga toxin unit has been achieved. The biological evaluation of this system is currently in process.

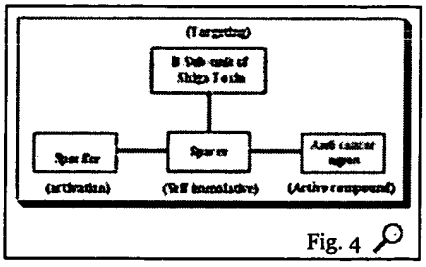

Fig. 4

4 Targeting and abiotic activation of prodrug. (J.-C. Florent, M. Azoulay). (Participants: W. Sallem)

The new approach we intend to explore is based on the possibility of vectoring, on the surface of a tumor cell, a monoclonal antibody bearing an azido group, i.e. a functionality which is "exogenous", abiotic and essentially unreactive towards biomolecules inside or on the cell surface. It is planed that the azido group will specifically recognize and react (Staudinger reaction) with an exogenous phosphine linked to a non-toxic prodrug. This encounter will promote a cascade of events resulting in the liberation of the cytotoxic drug.

We have realized the synthesis of a prodrug system wherein doxorubicin is linked to a self-immolative spacer involving a phosphine moiety. The prodrug is stable in pH 7 buffer, and rapidly releases the drug when a soluble azido-compound is added. In a cellular assay cellular test (in collaboration with B. Bauvois), it was found that the prodrug was not sufficiently stable throughout the duration of the experiment at the pH of the cell culture medium. To prevent this unexpected cytotoxicity, we are presently synthesizing new spacers.

III. Chemical synthesis of glycosphingolipid analogues to study the retrograde pathway and its involvement in cancer. (J.-C. Florent, F. Schmidt).

Participants : S. Tani, M. Tazi Mezalek. *(Collaboration L. Johannes, " Traficking and Signalling"Laboratory, UMR 144 CNRS/Institut-Curie).*

In order to validate the possible involvement of Gb3 in the transport and the functional activity of some intracellular proteins, it is essential to demonstrate their interaction with Gb3. In this context, we have synthesized globotriose Gb3. Starting with this oligoside, we are presently preparing glycosphingolipid analogues in order to realize three objectives: (i) isolation, and purification of proteins from tumor cell extracts which bind Gb3 attached to beads, (ii) preparation of glycoconjugates in order to obtain monoclonal antibodies by phage display (cDNA version), (iii) verification of the hypothesis that Gb3 is indeed the receptor of endogenous proteins; in this view, we are preparing glycosphingolipid analogs adapted to ionic microscopy experiments. The instrument permitting cell imagery at the molecular level is located at the Curie Institute, Orsay. (collaboration, A. Croisy, U 350 INSERM).

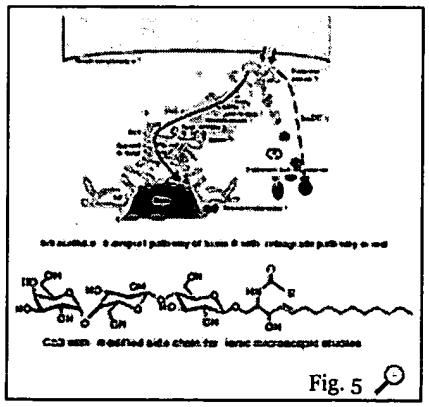

Fig. 5

IV. Targeting of topoisomerase inhibitors by formation of triple-helices in nucleic acids (D. Dauzonne).

Participants: P. Arimondo, F. Schmidt, S. Angenault. *(Collaboration: C. Hélène, U 201 INSERM; C. Bailly, U 524 INSERM; J. Tazi, UMR 5535).*

Our objective is to target topoisomerase inhibitors to gene targets selected for their implication in tumor cells proliferation (genes controlling cell cycle regulation/division, or anti-apoptotosis...). This targeting is based on the conjugation of a topoisomerase inhibitor to an oligonucleotide (TFO), which is able to selectively recognise a DNA sequence. Therefore it is conceivable to target this inhibitor against an area of selected genes by forming a triple-helix against a common sequence. By this way, irreversible lesions on these genes will inhibit their functions. According to the length or the sequence of the chosen nucleotide, selectivity may be enhanced (to target only one gene) or relaxed (to inhibit a group of genes).
Initially, oligonucleotide-inhibitor conjugates of topoisomerase I were prepared by covalently attaching two new campthothecin analogues prepared in our laboratory to the 3'-end of a16mer triple-helix forming oligonucleotide. The results obtained by our colleagues in MNHN demonstrated that it is *in vitro* possible to target these inhibitors to drive permanent site-specific cleavage in the region where the ligand was targeted. In the same prospect, we are now focusing on new podophyllotoxin derivatives synthesized by our group and endowed with potent topoisomerase II activity.

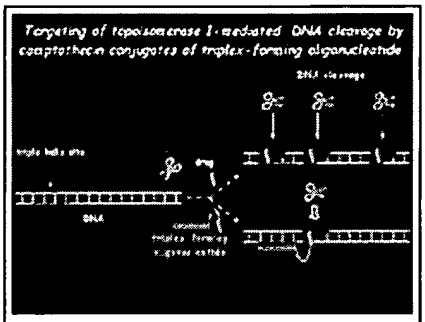

Fig. 6

Joint Project UMR 176 (Paris-Orsay)

Protein-Protein Interactions (E. Bertounesque, M. Croisy, D. Dauzonne, J-C Florent, D. Grierson). Participants : J-B. Bongui, M. Dorbec, T. Jullien-Lombrage,. Sindu Ros *(Collaborations : P. Hughes, UMR 2027 CNRS ; L. Aggerbeck, CGM, Gif-sur-Yvette, Pr. C. Garbay INSERM ; coordinater ACI Interaction protéine-protéine).*

Today, the conception of protein-protein interaction inhibitors constitutes a major challenge, and as a consequence there are enormous possibilities for discovery at both the fundamental and applied level.
In this context, we have initiated several federative projects within our department to synthesize molecules that inhibit protein-protein interactions. Simultaneously, we have established the necessary collaborations with biologists to evaluate the potential of these systems. The objective is to enrich the diversity of our compound collection, and in this way to target better its application.
For the first of these programmes "target directed organic synthesis" will be used to study two potentially important protein-protein interactions: i) the binding of the SH2 domain of Grb2 to phosphorylated tyrosine motifs present on the growth factors EGFR and erB2 which are implicated in the RAS signalling pathway, ii) the interaction of the p66 sub-unit of DNA polymerase δ with PCNA, for which the regulator is $p21^{wafi/CIP1}$.
The second programme involves a "diversity based organic synthesis" approach based upon the use of privileged scaffolds. The objective is to rapidily generate molecular diversity via, for instance, multicomponent reactions carried out in an automated parallel synthesis fashion.

The GrB2-SH2/EGFR or erB2 and PCNA-p66 Systems

In order to circumvent the problems inherent to the *in vivo* use of synthetic cyclic peptides which mime the micro domain in the GrB2-SH2 interaction we are looking toward the development of peptidomimetics which are more drug-like in their properties.
Concerning the search for molecules which mimc the inhibition by p21 of the p66-PCNA interaction, a single protein domain microchip developed by P. Hughes (UMR 2027 CNRS-IC) was used to screen the complete Curie compound collection. Between 30-40 hits were observed, 6 of which were subsequently confirmed as true p21 mimics by further biochemical tests. Following up on these results it was shown by molecular modeling that the active molecules interact with the PCNA-p66(p21) binding site. We are currently engaged in the construction of targeted libraries to optimise the specificity/activity of our best hits.

Parallel synthesis of γ-lactam 1-aryltetralones and polyfunctionalized flavone libraries.

Using thuriferic acid, obtained from natural lignane, as a privileged scaffold we have undertaken the synthesis of γ-lactam 1-aryltetralone based libraries. γ-Lactams display important pharmacological properties (psychotropic and anti-hypertension agents, peptidomimetics, non peptide mimics of somatostatin/sandostatin, anti-asthmatics, ...), but, relatively speaking, this sytem is not often encountered in natural products. In the context of this project, we have also constructed 1-aryltetraline libraries using parallel synthesis technology coupled to the use of scavenger resins. These libraries will be evaluated to identify protein-protein interaction inhibitors.
Flavones, known to interact with a wide range of proteins, represent an excellent privileged scaffold. Indeed, many diverse strategies can be envisaged to construct compound libraries based upon the flavone skeleton. In our programme we have chosen to elaborate new flavone containing molecules on solid support using an iterative/dendrimer type synthesis approach. In view of the large number of sites in these systems which can be modified, this approach will permit the simultaneous functionalization of several reaction sites in the same synthetic operation. A selection of the molecules for testing will be made as a function of their « size ».

Chimiothèque

The fruit of 30 years of research by the pharmacochemistry laboratory at Institut Curie has been brought together by the creation of the « chimiothèque de Curie/CNRS ». Our current library contains 6720 compounds formated in 96 well microplates. The intrinsic value of this library can be measured by its diversity (sulfur, oxygen and nitrogen based heterocycles and functionalized polyheterocycles, purines, flavones, sugars, steroids, porphyrins...), and by the fact that we have either conserved a stock of each component or the « know how » for its preparation. An up-date of the compound collection was initiated toward the end of 2003, and it is anticipated that the 2nd version of our chimiothèque will contain 8300 molecules.
The Curie compound library will soon be incorporated into the nationwide network, referred to as the « chimiothèque national », which was recently created by the CNRS and coordinated by Pr. Marcel Hibert, Strasbourg-Illkirch.
At present we have produced more than 20 copies of the collection, three of which were sold to industrial laboratories. Eighteen collaborative programmes, including five laboratories involved in ACI projects, have been established to test the collection, and several new candidate programmes are under review.
Screening programmes in the following areas have been realized:

1. dermatology
2. antimalaria

3. antibiotics
4. antivirals (HIV, and others)
5. inhibitors acting on the CNS
6. prion inhibitors
7. signalling pathway and cell cycle inhibitors
8. DNA targeted antitumor agents
9. rare forms of cancer
10. protein-protein interaction inhibitors

The results issuing from these collaborations are very encouraging. Indeed, for each test one or more molecules has been identified whose structure could/was not be predicted a priori. These results are the basis for a number of publications/patents, as well as the starting point for a number of lead optimization programmes.
The next step in the development of the Curie compound collection is to assure that it continues to grow thanks to the synthesis of new libraries displaying a large functional (drug like properties) and structural diversity. This implies the incorporation of rapid synthesis and molecular modeling modules into our « chimiothèque » platform. The rapid/automated synthesis module is an absolute requirement for the construction of new compound libraries on an optimal time scale, and it is planned that molecular modeling will play an important role in determining the content of the libraries to be constructed and in their virtual screening. Important inroads have been made this past year to consolidate our chimiothèque platform, as the Direction of Institut Curie has financed the creation of a « rapid synthesis » laboratory at our Orsay site. Several research projects will be developed in this new facility, and in particular the joint project within our department to develop potent protein-protein interaction inhibitors.

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Long QT Syndrome

Last Updated: June 10, 2005

Synonyms and related keywords: LQTS, congenital long QT syndrome, Romano-Ward syndrome, Jervell and Lange-Nielsen synd JLN syndrome, ventricular tachyarrhythmias, syncope, cardiac arrest, sudden death

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Disclosure

Background: Long QT syndrome (LQTS) is a congenital disorder characterized by a prolongation of the QT on electrocardiogram (ECG) and a propensity to ventricular tachyarrhythmias, which may lead to syncope, c arrest, or sudden death.

Pathophysiology: The QT interval on the ECG, measured from the beginning of the QRS complex to the e T wave, represents the duration of activation and recovery of the ventricular myocardium. Prolonged recove electrical excitation contributes to increased likelihood of dispersion of refractoriness, when some part of myocardium might be refractory to subsequent depolarization. Consequently, the wave of excitation may pu distinctive pathway around a focal point in myocardium (circus reentrant rhythm), leading to ventricular tachy hemodynamically ineffective contraction of the ventricles, syncope, and, possibly, sudden death. Heart rate corrected QTc values above 0.44 seconds generally are considered abnormal, although age- and sex-speci abnormal QTc values have been proposed.

LQTS has been recognized as the Romano-Ward syndrome (familial occurrence with autosomal dominant inheritance, QT prolongation, and ventricular tachyarrhythmias) or the Jervell and Lang-Nielsen (JLN) syndr (familial occurrence with autosomal recessive inheritance, congenital deafness, QT prolongation, and ventri arrhythmias).

LQTS is caused by mutations of cardiac ion channel genes; 6 chromosomal loci and 5 specific genes have l identified. Based on genetic background, 6 types of Romano-Ward syndrome and 2 types of JLN syndrome identified, as shown in Tables 1-2.

Table 1. Genetic Background of Inherited Forms of LQTS (Romano-Ward Syndrome)

LQTS Type	Chromosomal Locus	Mutated Gene	Ion Current Affected
LQT1	11p15.5	*KVLQT1* (*KCNQ1*) (heterozygotes)	Potassium current (I_{Ks})
LQT2	7q35-36	*HERG*	Potassium current (I_{Kr})
LQT3	3p21-24	*SCN5A*	Sodium current (I_{Na})
LQT4	4q25-27	?	?
LQT5	21q22.1-22.2	*KCNE1* (heterozygotes)	Potassium current (I_{Ks})
LQT6	21q22.1-22.2	*MiRP1*	Potassium current (I_{Kr})

Table 2. Genetic Background of Inherited Forms of LQTS (Jervell and Lang-Nielsen Syndrome)

LQTS Type	Chromosomal Locus	Mutated Gene	Ion Current Affected
JLN1	11p15.5	*KVLQT1* (*KCNQ1*) (homozygotes)	Potassium current (I_{Ks})
JLN2	21q22.1-22.2	*KCNE1* (homozygotes)	Potassium current (I_{Ks})

QT prolongation in LQTS is due to overload of myocardial cells with positively charged ions during ventricul repolarization. In LQT1, LQT2, LQT5, and LQT6 types, potassium ion channels are blocked or they open wi delay or are open for a shorter period than in normally functioning channels, leading to decreased potassiun outward current and prolonged repolarization. In LQT3, caused by mutations of the *SCN5A* sodium channel persistent inward sodium current contributes to prolonged repolarization.

LQT1, caused by *KVLQT1* I_{Ks} potassium channel gene mutations, and LQT2, caused by *HERG* I_{Kr} potassiu channel gene mutations, are estimated to account for the majority (87%) of cases of LQTS with known genc LQT3 accounts for 8%, whereas LQT5 and LQT6 are extremely rare, accounting for 5% of LQTS cases. Homozygous *KVLQT1* and *KCNE1* mutations are associated with congenital deafness (JLN syndrome) and for less than 1% of cases of LQTS. Approximately 200 different mutations of these genes have been found Significant phenotypic variation of the electrocardiographic findings (T wave morphology), factors triggering events, and risk of cardiac events exists, depending upon which gene and which mutations are involved. Be not all known cases of LQTS are caused by mutations of the above genes, other genes causing this disorde expected to be identified in the future.

Prolonged repolarization in people with LQTS predisposes to torsade de pointes (ie, polymorphic ventricular tachycardia), which may lead to ventricular fibrillation and sudden cardiac death. Heterogeneity of repolariz throughout the myocardium is an underlying substrate for this arrhythmia, which frequently is triggered by a premature ventricular beat, causing irregularity of the heart rate in a short-long-short sequence (ie, short cou interval of premature beat, subsequent long compensatory pause, and another short coupling interval of pre beat initiating episode of torsade de pointes). Torsade de pointes in patients with LQTS is very likely to self-terminate, which explains the relatively low overall lethality (risk of dying) of cardiac events.

Arrhythmic response in patients with LQTS can be precipitated by a variety of adrenergic stimuli, including e emotion, loud noise, and swimming, but it also may occur without such preceding conditions.

Drug-induced QT prolongation also may lead to increased risk of ventricular tachyarrhythmias (eg, torsade d pointes) and sudden cardiac death in a similar ionic mechanism as is observed in congenital LQTS.

Frequency:

- **In the US:** LQTS remains an underdiagnosed disorder, especially because at least 10-15% of LQTS g carriers have normal QTc duration.

  The prevalence of LQTS is difficult to estimate, but, based on the currently increasing frequency of dia LQTS may be expected to occur in 1 in 3000-5000 individuals.

- **Internationally:** The occurrence of LQTS internationally is similar to that in the United States.

Mortality/Morbidity:

- LQTS may lead to sudden cardiac death, which usually occurs in otherwise healthy young individuals. cumulative mortality rate reaches approximately 6% by age 40 years. The risk of sudden death from L higher in males than in females in people younger than 10 years; thereafter, risk is similar in males an females. The mortality rate is similar by genotype; however, lethality during a cardiac event is significa higher in patients with LQT3 than in patients with LQT1 and LQT2. Sudden death usually is caused by de pointes ventricular tachycardia and subsequent ventricular fibrillation.

- Ventricular tachyarrhythmias (usually torsade de pointes ventricular tachycardia) that complicate the c course of LQTS may lead to cardiac events, defined as syncope, cardiac arrest, or sudden death. Syn and especially aborted cardiac arrest, may lead to neurologic deficits. The risk of cardiac events is hig

males than in females before puberty and higher in females than in males after puberty. The risk of ca events is higher in patients with JLN1 and JLN2 than in patients with LQT1-LQT6. Among patients witl LQT6, those with LQT1 and LQT2 have a higher risk of cardiac events than those with LQT3 (LQT4-L(rare forms of LQTS).

Race: No clear evidence exists for race-related differences in the occurrence of LQTS.

Sex:

- More females (60-70% of cases) than males are diagnosed with new cases of LQTS. The female predominance may be related to a longer duration of QT corrected for heart rate using the Bazett form (QTc) in adult females than in males and to a higher mortality rate in young males. The occurrence of males and females is similar in families identified with LQTS.
- Pregnancy is not associated with a higher incidence of cardiac events, whereas the postpartum period associated with significantly increased risk of cardiac events. A higher incidence of correspondence of events with menses has been noted.

Age: Patients with LQTS usually present with cardiac events (ie, syncope, aborted cardiac arrest, sudden d a young age (ie, in childhood, adolescence, or early adulthood). The risk of death from LQTS is higher in bo in girls in children younger than 10 years, and risk is similar in males and females thereafter.

History: Patients with LQTS usually are diagnosed after a cardiac event (eg, syncope, cardiac arrest) alrea occurred. In some situations, LQTS is diagnosed after sudden death in family members. Some individuals a diagnosed with LQTS based on an ECG showing QT prolongation.

- A history of cardiac events is the most typical clinical presentation in patients with LQTS. Events may l triggered by exercise, swimming, or emotion, but they also may occur during night sleep. Triggering e\ somewhat different by genotype. Patients with LQT1 usually experience cardiac events preceded by e or swimming, patients with LQT2 may experience arrhythmic events after both emotion and exercise, ; patients with LQT3 usually experience events during night sleep.
- Obtain information about hearing loss (deficit) in a patient and his or her family members to determine possibility of JLN.
- Information about medication taken is critical for the differential diagnosis of congenital LQTS and drug induced QT prolongation (which also may have genetic background). The list of drugs that may affect repolarization and/or cause torsades de pointes can be found at ArizonaCERT.
- A family history of cardiac arrest and sudden death, especially at a young age, may suggest a congen (familial) form of LQTS.
- The analysis of repolarization duration (QTc) and morphology in the patient's ECG findings and in EC(findings of the patient's relatives frequently leads to proper diagnosis.

Physical: The findings on physical examination usually are not indicative of LQTS diagnosis, although som patients may present with excessive bradycardia for their age, and some patients may have hearing loss (c

deafness), indicating the possibility of JLN. Also, perform the physical examination to exclude other potentia reasons for arrhythmic and syncopal events in otherwise healthy people (eg, heart murmurs caused by hype cardiomyopathy, valvular defects).

Causes: Details of the genetic background of LQTS are presented in Pathophysiology. LQTS is caused by mutations of genes encoding cardiac ion channel proteins, causing abnormal ion channel kinetics. Shortenir potassium channel opening in LQT1, LQT2, LQT5, LQT6, JLN1, and JLN2 and the delayed closing of a sod channel in LQT3 cause the overcharge of a myocardial cell with positive ions.

Secondary (drug-induced) QT prolongation also may have a genetic background, consisting of predispositio ion channel to abnormal kinetics caused by gene mutation or polymorphism. However, data are not sufficier claim that all patients with drug-induced QT prolongation have a genetic LQTS-related mechanism. The list that may affect repolarization and/or cause torsades de pointes can be found at ArizonaCERT.

DIFFERENTIALS

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Sudden Cardiac Death
Syncope

Other Problems to be Considered:

Drug-induced QT prolongation
QT prolongation in the course of other diseases (eg, myocardial infarction, cerebral hemorrhage)
Vasovagal syncope
Seizures
Other causes of syncope, cardiac arrest, or sudden death in otherwise healthy people include hypertrophic cardiomyopathy, Brugada syndrome, and arrhythmogenic right ventricular dysplasia.

WORKUP

S

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Lab Studies:

- Routinely check serum levels of potassium (and sometimes magnesium) in patients presenting with Q arrhythmic events to eliminate secondary reasons for repolarization abnormalities.
- Genetic testing for known mutations in DNA samples from studied patients is becoming more accessit Identification of an LQTS gene mutation confirms the diagnosis; however, a negative result on genetic value because only approximately 50% of patients with LQTS have known mutations, and the remaini may have mutations of yet unknown genes.

Imaging Studies:

- Imaging studies (eg, echocardiography, MRI) may serve only to exclude other potential reasons for ar hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia).

Other Tests:

- Standard ECG recordings and analysis of QTc duration and T wave morphology are the most useful te

prolongation of the QTc interval is defined based on age-specific and sex-specific criteria. The QTc, cc calculated by dividing the measured QT by the square root of the R-R interval, both of which are meas prolongation greater than 0.46 seconds indicates a high likelihood of LQTS diagnosis (see Image 1). H 15% of gene-positive patients with LQTS present with QTc duration within the reference range (see Im

Table 3. Definition of the QTc Interval Based on Age-Specific and Sex-Specific Criteria

Age and Sex	Prolonged QTc (Seconds)	Borderline QTc (Seconds)	Reference Range (Seconds)
Children (<15 y)	>0.46	0.44-0.46	<0.44
Adult males	>0.45	0.43-0.45	<0.43
Adult females	>0.46	0.45-0.46	<0.45

- In patients with suggested LQTS with borderline QTc values (or even values within the reference rang analysis of dynamic behavior of QTc duration during exercise ECG testing or long-term Holter monitor of the QT interval duration to the changing heart rate, with evident QTc prolongation at a faster heart r rarely are observed during exercise testing or Holter recordings in patients with LQTS.
- No evidence indicates that invasive electrophysiology testing with attempts to induce ventricular tachy
- Detection of visible T wave alternans in patients with LQTS indicates increased risk of cardiac arrhythr and ventricular fibrillation).
- Detection of microvolt T wave alternans has low sensitivity and high specificity in diagnosing LQTS. Th microvolt T wave alternans has not been studied systematically.

TREATMENT

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Medical Care:

- Beta-blockers are drugs of choice for patients with LQTS. The protective effect of beta-blockers is rela blockade diminishing the risk of cardiac arrhythmias.
- Although for years the recommended dose of beta-blockers was relatively large (ie, **propranolol** 3 mg individual]), recent data suggest that smaller doses have a protective effect similar to that of large dos
- Beta-blockers are effective in preventing cardiac events in approximately 70% of patients, while cardia despite beta-blocker therapy in the remaining 30% of patients.
- **Propranolol** and nadolol are the most frequently used beta-blockers, although atenolol and metoprolc patients with LQTS. Different beta-blockers demonstrate similar effectiveness in preventing cardiac ev
- No gene or gene-specific therapy is approved clinically, although the safety of gene-specific therapy d blockers in LQT3, potassium supplementation with spironolactones in LQT2) currently is undergoing e of Health (NIH)–sponsored trials.
- Implantation of cardioverter-defibrillators appears to be the most effective therapy for high-risk patients aborted cardiac arrest or recurrent cardiac events despite conventional therapy (ie, beta-blocker alone combination with pacemaker and/or stellectomy may be used.

- Implantation of cardiac pacemakers (with ventricular or dual chamber pacing) has been considered a l based on the premise that pacing eliminates arrhythmogenic bradycardia, decreases heart rate irregul short series), and decreases repolarization heterogeneity, therefore diminishing the risk of torsade de tachycardia. However, recent data indicate that cardiac events continue to occur in high-risk patients v newer models of implantable cardioverter-defibrillators have a cardiac-pacing function included, cardia defibrillators) is likely to be used less often in patients with LQTS.

- Left cervicothoracic stellectomy is another antiadrenergic therapeutic measure used in high-risk patien those with recurrences of cardiac events despite beta-blocker therapy. Stellectomy decreases the risk patients with LQTS.

- In some high-risk patients, combination therapy consisting of beta-blockers, stellectomy, and implanta with cardiac pacing function is used.

Consultations:

- Typically, consult a cardiologist and cardiac electrophysiologist when evaluating patients with LQTS.

- In families of patients with genotypically confirmed LQTS, genetic counseling of patients and family me

Activity: Because cardiac events in LQTS patients frequently are triggered by physical activity, swimming, a discourage competitive sports.

No causative treatment of LQTS exists. Antiadrenergic therapeutic measures (eg, beta-blockers, left cervicc device therapy (eg, pacemakers, implantable cardioverter-defibrillators) aim to decrease the risk and lethalit

Drug Category: *Beta-adrenergic blocking agents* -- Antiadrenergic therapy effectively protects most pa blockers, especially **propranolol**, are the most frequently used drugs in patients with LQTS. Inform patients beta-blockers should be continued indefinitely and should not be stopped. Interruption in beta-blocker therap of cardiac events.

Drug Name	**Propranolol** (Inderal) -- Decreases effect of sympathetic stimulation on the heart. Decreases conduction through the AV node and has negative chronotropic and inotropic effects. Consult a cardiologist because dosing practice is variable and individualized in patients with LQTS. Patients with asthma should use cardioselective beta-blockers. Patients with LQTS who are unable to take beta-blockers may require implantation of cardioverter-defibrillators as first-line therapy.
Adult Dose	2-3 mg/kg/d PO
Pediatric Dose	Administer as in adults
Contraindications	Documented hypersensitivity; uncompensated congestive heart failure, bradycardia, cardiogenic shock, AV conduction abnormalities
Interactions	Coadministration with aluminum salts, barbiturates, NSAIDs, penicillins, calcium salts, cholestyramine, and rifampin may decrease **propranolol** effects; cimetidine, loop diuretics, and MAOIs may increase toxicity of **propranolol**; toxicity of hydralazine, haloperidol, benzodiazepines, and phenothiazines may increase with **propranolol**; **cardiotoxicity** may increase when administered concurrently with calcium channel blockers, quinidine, flecainide, and digoxin (all affect conduction)
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Beta-adrenergic blockade may decrease signs of acute hypoglycemia and hyperthyroidism; abrupt withdrawal may exacerbate symptoms of hyperthyroidism, including thyroid storm; withdraw drug slowly and monitor closely; should be taken by pregnant women with LQTS during pregnancy and during the postpartum period when risk of cardiac events increases
Drug Name	Nadolol (Corgard) -- Prescribed frequently because of its long-term effect. Decreases effect of sympathetic stimulation on the heart. Decreases conduction through the AV node and has negative chronotropic and inotropic effects. Consult a cardiologist because dosing practice is variable and individualized in patients with LQTS. Patients with asthma should use cardioselective beta-blockers. Patients with LQTS who are unable to take beta-blockers may require implantation of cardioverter-defibrillators as first-line therapy.
Adult Dose	2-3 mg/kg/d PO
Pediatric Dose	Administer as in adults
Contraindications	Documented hypersensitivity; uncompensated congestive heart failure, bradycardia, asthma, cardiogenic shock, AV conduction abnormalities
Interactions	Aluminum salts, barbiturates, NSAIDs, penicillins, calcium salts, cholestyramine, and rifampin may decrease bioavailability and plasma levels, possibly resulting in decreased pharmacologic effects; toxicity may increase with coadministration of sparfloxacin, phenothiazines,

	calcium channel blockers, quinidine, flecainide, and oral contraceptives; may increase toxicity of digoxin, flecainide, clonidine, epinephrine, nifedipine, prazosin, verapamil, and lidocaine
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Beta-adrenergic blockade may decrease signs of acute hypoglycemia and hyperthyroidism; abrupt withdrawal may exacerbate symptoms of hyperthyroidism, including thyroid storm; withdraw drug slowly and monitor closely; should be taken by pregnant women with LQTS during pregnancy and the postpartum period when risk of cardiac events increases
Drug Name	Metoprolol (Lopressor) -- Selective beta1-adrenergic receptor blocker that decreases automaticity of contractions. During IV administration, carefully monitor blood pressure, heart rate, and ECG. Patients with LQTS who are unable to take beta-blockers may require implantation of cardioverter-defibrillators as first-line therapy. Consult a cardiologist because dosing practice is variable and individualized in patients with LQTS.
Adult Dose	2-3 mg/kg/d PO
Pediatric Dose	Administer as in adults
Contraindications	Documented hypersensitivity; uncompensated congestive heart failure, bradycardia, asthma, cardiogenic shock, AV conduction abnormalities
Interactions	Aluminum salts, barbiturates, NSAIDs, penicillins, calcium salts, cholestyramine, and rifampin may decrease bioavailability and plasma levels of metoprolol, possibly resulting in decreased pharmacologic effects; toxicity of metoprolol may increase with coadministration of sparfloxacin, phenothiazines, astemizole **(recalled from US market)**, calcium channel blockers, quinidine, flecainide, and contraceptives; metoprolol may increase toxicity of digoxin, flecainide, clonidine, epinephrine, nifedipine, prazosin, verapamil, and lidocaine
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Category D in third trimester of pregnancy; beta-adrenergic blockade may reduce signs and symptoms of acute hypoglycemia and may decrease clinical signs of hyperthyroidism; abrupt withdrawal may exacerbate symptoms of hyperthyroidism, including thyroid storm; monitor patient closely and withdraw drug slowly; during IV administration, carefully monitor blood pressure, heart rate, and ECG
Drug Name	Atenolol (Tenormin) -- Selectively blocks beta1-receptors with little or no affect on beta 2 types. Patients with LQTS who are unable to take beta-blockers may require implantation of cardioverter-defibrillators as first-line therapy. Consult a cardiologist because dosing practice is variable and individualized in patients with LQTS.
Adult Dose	2-3 mg/kg/d PO
Pediatric Dose	Administer as in adults
Contraindications	Documented hypersensitivity; congestive heart failure, pulmonary edema, cardiogenic shock, AV conduction abnormalities, heart block (without a pacemaker)

Interactions	Coadministration with aluminum salts, barbiturates, calcium salts, cholestyramine, NSAIDs, penicillins, and rifampin may decrease effects; haloperidol, hydralazine, loop diuretics, and MAOIs may increase toxicity of atenolol
Pregnancy	D - Unsafe in pregnancy
Precautions	Beta-adrenergic blockade may reduce symptoms of acute hypoglycemia and mask signs of hyperthyroidism; abrupt withdrawal may exacerbate symptoms of hyperthyroidism and cause thyroid storm; monitor patients closely and withdraw drug slowly; during IV administration, carefully monitor BP, heart rate, and ECG

Further Inpatient Care:

- After recent cardiac events (eg, syncope, cardiac arrest), patients with LQTS frequently are hospitalize enable immediate rescue if cardiac arrhythmias recur.
- Asymptomatic individuals with LQTS usually do not require hospitalization; however, carefully evaluate care in ambulatory conditions.

Further Outpatient Care:

- A cardiologist or electrophysiologist should see patients with LQTS on a regular basis.

Deterrence/Prevention:

- Antiadrenergic therapy (eg, beta-blockers, stellectomy) aims to prevent future cardiac events.
- Use implantable cardioverter-defibrillators to prevent sudden cardiac death in patients with LQTS who tachyarrhythmias.
- Educate family members of patients with LQTS regarding the disorder and the basics of cardiopulmon Sudden Arrhythmia Death Syndromes (SADS) and Cardiac Arrhythmias Research and Education (CA groups for families with LQTS.
- Educate patients and family members about medications that may induce QT prolongation and that sh with LQTS. The most updated list of such medication can be viewed at ArizonaCERT.
- Anesthetics/asthma medication - Epinephrine (Adrenaline) for local anesthesia or as an asthma medic
- Antihistamines
    - Terfenadine (Seldane **[recalled from US market]**) for allergies
    - Astemizole (Hismanal **[recalled from US market]**) for allergies
    - Diphenhydramine (Benadryl) for allergies
- Antibiotics

- Erythromycin (E-Mycin, EES, EryPed, PCE) for lung, ear, and throat infections
- Trimethoprim and sulfamethoxazole (Bactrim, Septra) for urinary, ear, and lung infections
- Pentamidine (Pentam, intravenous) for lung infections

- Heart medications
  - Quinidine (Quinidine, Quinidex, Duraquin, Quinaglute) for heart rhythm abnormalities
  - Procainamide (Pronestyl) for heart rhythm abnormalities
  - Disopyramide (Norpace) for heart rhythm abnormalities
  - Sotalol (Betapace) for heart rhythm abnormalities
  - Probucol (Lorelco) for high triglycerides, cholesterol
  - Bepridil (Vascor) for chest pain (angina)
- Gastrointestinal medications - Cisapride (Propulsid) for esophageal reflux, acid indigestion
- Antifungal drugs
  - Ketoconazole (Nizoral) for fungal infections
  - Fluconazole (Diflucan) for fungal infections
  - Itraconazole (Sporanox) for fungal infections
- Psychotropic drugs
  - Amitriptyline, tricyclics (Elavil, Norpramin, Viractil) for depression
  - Phenothiazine derivatives (Compazine, Stelazine, Thorazine) for mental disorders
  - Haloperidol (Mellaril, Etrafon, Trilafon, others) for mental disorders
  - Risperidone (Haldol) for mental disorders
  - Pimozide (Risperdal) for mental disorders
- Medications for potassium loss
  - Indapamide (Lozol) for water loss, edema
  - Other diuretics
  - Medications for vomiting and diarrhea

Complications:

- Sudden cardiac death is the most devastating complication of the disorder, especially because it frequ individuals.
- Neurologic deficits after aborted cardiac arrest may complicate the clinical course after successful resu

Prognosis:

- Prognosis in patients with LQTS treated with beta-blockers (and other therapeutic measures if needed episodes of torsades de pointes usually are self-terminating in patients with LQTS; only approximately fatal.
- Patients at high risk (those with aborted cardiac arrest or recurrent cardiac events despite beta-blocke increased risk of sudden death; treat these patients with implantable cardioverter-defibrillators. Prognc cardioverter-defibrillators is very good.

Patient Education:

- Educate patients regarding the nature of the syndrome and factors that trigger cardiac events. Patient: (eg, alarm clock), strenuous exercise, water activities, and other arousal factors.
- Educate patients and family members about the critical importance of systematic treatment with beta-b
- Advise family members (also teachers at school) to undergo training in CPR.

MISCELLANEOUS

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Medical/Legal Pitfalls:

- Failure to diagnose LQTS when QTc clearly is prolonged
- Failure to treat patients with LQTS with beta-blockers, unless contraindicated
- Failure to educate patients and family members about potential risks associated with strenuous sport a with interruption of beta-blocker therapy
- Failure to screen for LQTS in family members of proband (first family member with the disease)

PICTURES

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Caption: Picture 1. Marked prolongation of QT interval in a 15-year-old boy with long QT syndrome (R-R=1.00 s, QT=0.56 s, QTc=0.56 s). Abnormal morphology of repolarization can be observed in almost every lead (ie, peaked T waves, "bowing" ST segment). Bradycardia is a common feature in patients with long QT syndrome.


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